Safety of a feed additive consisting of semduramicin sodium (Aviax 5%) for chickens for fattening (Phibro Animal Health s.a.)

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), Vasileios Bampidis, Giovanna Azimonti, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Mojca Fasmon Durjava, Maryline Koubia, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa, Ruud Woutersen, Georges Bories, Pier Sandro Cocconcelli, Antonio Finizio, Jürgen Gropp, Guido Rychen, Ivana Teodorovic, Rosella Brozzi, Orsolya Holczknecht, Elisa Pettenati, Joana Revez and Maria Vittoria Vettori

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 the coccidiostat Aviax 5% (semduramicin sodium) when used in feed for chickens for fattening. In a previous assessment, the FEEDAP Panel could not conclude on the taxonomical identification of the production strain at species level and on the absence of genetic determinants for antimicrobial resistance. In addition, the Panel could not conclude on the safety for the target animals and could not set maximum residue limits to protect consumers. Regarding the safety for the environment, although the use of the additive was considered safe for the terrestrial compartment, a risk for the aquatic compartment and for groundwater pollution could not be excluded. Based on the new data provided, the FEEDAP Panel concludes that there are no safety concerns for the target animals, consumer, user and environment regarding the production strain of semduramicin sodium. Based on the results in the tolerance trial, the FEEDAP Panel concludes that the additive is safe for chickens for fattening up to the maximum recommended level (25 mg/kg complete feed), but no margin of safety can be established. The use of semduramicin sodium at a maximum level of 25 mg/kg complete feed for chickens for fattening is safe for consumers with no withdrawal time. Based on the new data provided and the current requirements for environmental risk assessment, the use of semduramicin sodium from Aviax 5% in feed for chickens for fattening up to 25 mg/kg complete feed does not pose a risk for groundwater nor for aquatic and sediment compartments, while a risk for the terrestrial compartment cannot be excluded. The bioaccumulation and the risk for secondary poisoning are considered to be low.

© 2022 Wiley-VCH Verlag GmbH & Co. KgaA on behalf of the European Food Safety Authority.

Keywords: coccidiostats and histomonostats, semduramicin sodium, chickens for fattening, safety

Requestor: European Commission
Question number: EFSA-Q-2019-00813
Correspondence: feedap@efs.europa.eu
Panel members: Vasileios Bampidis, Giovanna Azimonti, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Mojca Fašmon Durjava, Maryline Kouba, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa and Ruud Woutersen.

Legal notice: Relevant information or parts of this scientific output have been blackened in accordance with the confidentiality requests formulated by the applicant pending a decision thereon by the European Commission. The full output has been shared with the European Commission, EU Member States and the applicant. The blackening will be subject to review once the decision on the confidentiality requests is adopted by the European Commission.

Declarations of interest: If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

Acknowledgements: The Panel wishes to acknowledge the contribution to this opinion of Montserrat Anguita, Jaume Galobart, Barbara Rossi and Jordi Tarrés-Call and the following Working Groups of the FEEDAP Panel: WG on Animal Nutrition, WG on Microbiology, WG on Environment and WG on Toxicology.

Suggested citation: EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Bampidis V, Azimonti G, Bastos ML, Christensen H, Dusemund B, Fasmon Durjava M, Kouba M, López-Alonso M, López Puente S, Marcon F, Mayo B, Pechova A, Petkova M, Ramos F, Sanz Y, Villa RE, Woutersen R, Bories G, Cocconcelli PS, Finizio A, Gropp J, Rychen G, Teodorovic I, Brozzi R, Holczknecht O, Pettenati E, Revez J and Vettori MV, 2022. Scientific Opinion on the safety of a feed additive consisting of semduramicin sodium (Aviax 5%) for chickens for fattening (Phibro Animal Health s.a.). EFSA Journal 2022;20(8):7432, 17 pp. https://doi.org/10.2903/j.efsa.2022.7432

ISSN: 1831-4732

© 2022 Wiley-VCH Verlag GmbH & Co. KgaA on behalf of the European Food Safety Authority.

This is an open access article under the terms of the Creative Commons Attribution-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited and no modifications or adaptations are made.

The EFSA Journal is a publication of the European Food Safety Authority, a European agency funded by the European Union.
Table of contents

Abstract...................................................................................................................................................... 1
1. Introduction........................................................................................................................................ 4
1.1. Background and Terms of Reference as provided by the requestor............................................... 4
2. Data and methodologies..................................................................................................................... 4
2.1. Data.............................................................................................................................................. 4
2.2. Methodologies............................................................................................................................... 4
3. Assessment....................................................................................................................................... 4
3.1. Characterisation of the production organism................................................................................. 5
3.2. Safety ......................................................................................................................................... 5
3.2.1. Safety of the production strain ................................................................................................. 5
3.2.2. Safety for the target species ..................................................................................................... 5
3.2.3. Safety for the consumer ........................................................................................................... 7
3.2.3.1. Conclusions on safety for the consumer.................................................................................. 7
3.2.4. Safety for the environment ...................................................................................................... 7
3.2.4.1. Phase I................................................................................................................................... 8
3.2.4.2. Phase II................................................................................................................................. 9
3.2.4.3. Conclusions on safety for the environment.............................................................................. 12
4. Conclusions..................................................................................................................................... 12
5. Documentation as provided to EFSA/chronology............................................................................. 13
References............................................................................................................................................... 13
Abbreviations ......................................................................................................................................... 14
Appendix A – Detailed results on chronic exposure calculation.............................................................. 15
1. Introduction

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

Regulation (EC) No 1831/2003 establishes rules governing the Community authorisation of additives for animal nutrition and, in particular, Article 9 defines the terms of the authorisation by the Commission.

The applicant, Phibro Animal Health s.a., is seeking a Community authorisation of semduramicin sodium as a feed additive to be used as a coccidiostat for chickens for fattening. (Table 1)

Table 1: Description of the substances

| Category of additive           | Coccidiostats and histomonostats |
|--------------------------------|----------------------------------|
| Functional group of additives | Coccidiostats and histomonostats |
| Description                   | Semduramicin sodium              |
| Target animal category        | Chickens for fattening           |
| Applicant                     | Phibro Animal Health s.a.        |
| Type of request               | New opinion                      |

On 14 June 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 and efficacy of the product, could not conclude on the characterisation of the active substance, safety for the target species and consumers, and on a risk for the aquatic compartment and groundwater.

The Commission gave the possibility to the applicant to submit complementary information in order to complete the assessment and to allow a revision of Authority’s opinion. The new data have been received on 13 November 2019.

In view of the above, the Commission asks the Authority to deliver a new opinion on semduramicin sodium as a feed additive for chickens for fattening based on the additional data submitted by the applicant.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of additional information1 to a previous application of the same product.2

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, peer-reviewed scientific papers, other scientific reports and experts’ elicitation knowledge, to deliver the present output.

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of semduramicin sodium (Aviax 5%) is in line with the principles laid down in Regulation (EC) No 429/20083 and the relevant guidance documents: Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, 2018a), Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017a), Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017b) and Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019).

3. Assessment

The additive Aviax 5% is a preparation of the polyether ionophore semduramicin sodium produced by fermentation of Actinomadura spp. (ATCC 53664) (semduramicin mycelium) and is intended to be

---

1 FEED dossier reference: FAD-2019-0073.
2 FEED dossier reference: FAD-2014-0009 and FAD-2015-0037.
3 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.
used as a coccidiostat in feed for chickens for fattening at a level of 20–25 mg semduramicin sodium/kg complete feed.

In the previous opinion (EFSA FEEDAP Panel, 2018b), the Panel could not conclude on the taxonomical identification of the production strain at species level and on the absence of genetic determinants for antimicrobial resistance. In addition, the Panel could not conclude on the safety for the target animals and could not set maximum residue limits (MRLs) to protect consumers. Finally, as regards the safety for the environment, although the use of the additive was considered safe for the terrestrial compartment, a risk for the aquatic compartment and for groundwater pollution could not be excluded.

The applicant has now submitted additional data to cover the limitations identified in the previous opinion which are assessed below. The applicant also proposed to reduce the withdrawal time from 1 to 0 days.

3.1. Characterisation of the production organism

In its previous opinion (EFSA FEEDAP Panel, 2018b), the Panel concluded that ‘The approaches used for taxonomical identification consistently place the strain ATCC 53664 in the genus *Actinomadura* but cannot unequivocally assign it to a valid taxonomic species of this genus, suggesting that the strain belonged to a new species within the genus *Actinomadura*. The FEEDAP Panel cannot conclude on the absence of genetic determinants for antimicrobial resistance in *Actinomadura* spp. ATCC 53664’.

The production strain is a mutant of strain ATCC 53666 and has not been genetically modified. The applicant has provided data that allowed the allocation of the production strain as the type strain of the recently-described species *Actinomadura roseirufa* (Wieme et al., 2019). The taxonomical identification and the assignment to a new species was achieved by the analysis of the whole genome sequence (WGS) of the production strain and its comparison (digital DNA–DNA hybridisation and average nucleotide identity) with closely related species of the *Actinomadura* genus (Wieme et al., 2019). The production strain is deposited in the American Type Culture Collection under the accession number ATCC 53664^T^.

The susceptibility of *A. roseirufa* ATCC 53664^T^ to the list of antibiotics recommended by the FEEDAP Panel for Gram-positive bacteria (EFSA FEEDAP Panel, 2018b) was tested and thus, of no concern.

The WGS of the production strain was interrogated for antimicrobial resistance genes and no genes of concern were identified.

Based on the additional data submitted and described above, the Panel considers that the data gaps identified in the previous opinion have been properly addressed.

3.2. Safety

3.2.1. Safety of the production strain

The production organism was identified as *A. roseirufa* strain ATCC 53664^T^ and was proven not to harbour any acquired antimicrobial resistance genes. The Panel notes that the WGS of the production strain was not queried for virulence factors. Considering that the product is free from viable cells (EFSA FEEDAP Panel, 2018b), the Panel considers that this does not represent a concern. Consequently, the Panel concludes that there are no safety concerns for the target animal, consumer, user and environment regarding the production strain of semduramicin sodium.

3.2.2. Safety for the target species

In its former opinion (EFSA FEEDAP Panel, 2018b), the FEEDAP Panel could not conclude on the safety of the additive for the target species as none of the tolerance studies submitted were
performed according to recent EU requirements and did not include haematology, blood biochemistry and pathological examination. The applicant performed a new tolerance study with the additive semduramicin sodium (Aviax 5%) in line with the Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017a). A total of 210 one-day-old male chickens for fattening (Ross 308) were randomly allocated to three groups with seven pens of 10 animals each. The groups were fed the same basal diet based on maize and soybean meal in crumble form during the whole study period of 35 days. The basal diet was either not supplemented (control) or supplemented with semduramicin sodium from Aviax 5% to provide 25 mg (1× maximum recommended level), or 75 mg (3×) per kg complete feed. The analysed values were 27.3 and 81.2 mg/kg complete feed, respectively. Feed and water were offered on ad libitum basis. Health status was monitored daily. Animals were weighed per pen at the beginning and the end of the study, feed intake was registered per pen by the end of study and feed to gain ratio was calculated accordingly. At the end of the study, two birds per pen were randomly selected for blood sampling and necropsy. Haematology and blood biochemistry parameters were determined. Gross pathology including organ weight (liver and kidney) and liver histopathology was performed. A one-way analysis of variance was done with the data using as experimental unit the pen for performance data and the animal for blood biochemistry, haematology and organ weights. Group means were compared with Dunnett’s test and/or Tukey’s test. Categorical data were examined by the Fisher exact test. Significance level was set at 0.05 for two-sided tests.

The main results of performance parameters are summarised in Table 2.

### Table 2: Effect of Aviax 5% on the performance of chickens for fattening in a 35-day tolerance study

| Groups semduramicin sodium (mg/kg) | Daily feed intake (g) | Final body weight (g) | Body weight gain (g/day) | Feed to gain ratio |
|-----------------------------------|-----------------------|-----------------------|--------------------------|--------------------|
| 0                                 | 81⁴                   | 2,110⁴                | 59⁴                     | 1.37⁴              |
| 25                                | 79⁴                   | 2,040⁴                | 57⁴                     | 1.39⁴              |
| 75                                | 72⁵                   | 1,660⁵                | 46⁵                     | 1.55⁵              |

⁴,⁵ Mean values within a column with a different superscript are significantly different p < 0.05.

No mortality was observed during the study. The birds that received a diet supplemented with the additive at the maximum use level did not show any significant difference from the control group. However, the birds receiving threefold the maximum recommended dose showed lower feed intake, lower average body weight gain and lower final body weight compared to the control and the maximum level group (1×) and a worse feed to gain ratio compared to the control.

Considering haematology and blood biochemistry, no significant differences were observed between the control and the maximum recommended level group. Several significant differences from the control were found in the overdose group, i.e. a decrease in total proteins, albumin and globulins, ALP, K, RBC, HCT; an increase of cholesterol, MCHC and monocytes.

No macroscopic lesions were observed during necropsy, except some pale livers (steatosis) in animals belonging to all groups. Histopathological examination of liver tissue (of two control livers, six and eight livers of the use level and overdose group, respectively) showed some findings which were mostly related to the macroscopic findings (steatosis).

The overdose also resulted in a significant decrease of absolute weights of liver and kidney compared to the control and the use level group. An assessment of the organ weights relative to body weight was not possible since the birds taken for necropsy were not individually weighed.

---

8 Technical dossier/Annex 3 and Supplementary information July 2020 Attachment 2.
9 The feed contained by calculation 23% crude protein, 6% crude fat, 0.5% methionine and 12 MJ ME/kg.
10 Erythrocytes (RBC), haematocrit (HCT), haemoglobin (HGB), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), leucocytes (WBC), neutrophils (heterophils) (NEU and %NEU), lymphocytes (LYM and %LYM), monocytes (MONO and %MONO), eosinophils (EOS and %EOS), basophils (BASO and %BASO), platelets (PLT), calcium (Ca), total proteins (TP), albumin (ALB), globulin (GLOB), albumin/globulin, uric acid (UREA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALKP), cholesterol (CHOL), sodium (Na), potassium (K), sodium/potassium, chloride (Cl).
11 Since body weight of the birds used for necropsy was not available, the pen average was used to estimate the relation of liver weight to body weight. The estimate figures did not indicate a specific effect of the additive overdose on liver weight, the estimated relative liver weights were similar for all three experimental groups.
Conclusions on the safety for the target species

Based on the results in the tolerance trial, the FEEDAP Panel concludes that the additive is safe for chickens for fattening up to the maximum recommended level, but no margin of safety can be established.

3.2.3. Safety for the consumer

In its former opinion (EFSA FEEDAP Panel, 2018b), the FEEDAP Panel confirmed that the acceptable daily intake (ADI) of 0.00125 mg/kg set for the crystalline semduramicin was applicable also to mycelial semduramicin and that semduramicin is the marker residue.

In 2018, the exposure of consumers to semduramicin-related total residues present in tissues was calculated according to daily food consumption values of animal products set in Regulation (EC) No 429/2008 and a withdrawal time of 1 day was confirmed. MRLs were considered necessary but could not be set due to lack of data for marker residue concentrations after 24 h withdrawal and limited sensitivity of the analytical method.

For the current assessment, the applicant recalculated the exposure using the methodology described in the Guidance on the safety of feed additives for consumers (EFSA FEEDAP Panel, 2017b) and proposed a withdrawal time of 0 day.

Using the same semduramicin-related total residue data reported in the 2018 opinion (EFSA FEEDAP Panel, 2018b), the chronic exposure of consumers to residues measured after 6 h – which corresponds to practically 0-day withdrawal time – was calculated using European food consumption data of different age classes from EFSA’s Comprehensive European Food Consumption Database as detailed in the Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017b). The outcome of the calculation is reported in Table 3 (for further details see Appendix A, Table A.1).

Table 3: Chronic exposure of consumers to semduramicin-related total residues based on data at 6 h withdrawal time in chicken tissues

| Population class     | Number of surveys | Highest exposure estimate (µg/kg bw per day) | % ADI |
|----------------------|------------------|---------------------------------------------|-------|
| Infants              | 6                | 0.25                                        | 20    |
| Toddlers             | 10               | 0.44                                        | 35    |
| Other children       | 18               | 0.60                                        | 48    |
| Adolescents          | 17               | 0.16                                        | 13    |
| Adults               | 17               | 0.53                                        | 42    |
| Elderly              | 14               | 0.10                                        | 8     |
| Very elderly         | 12               | 0.22                                        | 18    |

bw: body weight.

Exposures for all age classes were < 48% of the ADI; therefore, the FEEDAP Panel concludes that no withdrawal time is needed, and consequently, the setting of MRLs is considered not necessary.

3.2.3.1. Conclusions on safety for the consumer

The use of semduramicin sodium at a maximum level of 25 mg/kg complete feed for chickens for fattening is safe for consumers with no withdrawal time.

3.2.4. Safety for the environment

In its previous opinion, the Panel concluded that ‘Aviax 5% used in feed for chickens for fattening up to 25 mg/kg complete feed does not pose a risk for the terrestrial compartment. A risk for the aquatic compartment and for groundwater pollution cannot be excluded’ (EFSA FEEDAP Panel, 2018b). This evaluation was performed according to the principles set in the Technical Guidance for assessing the safety of feed additives for the environment (EFSA, 2008). For the current assessment, the
applicant submitted new experimental data and updated the environmental risk assessment following the requirements of the FEEDAP guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019).

### 3.2.4.1. Phase I

#### Physico-chemical properties of semduramicin

The physico-chemical properties of semduramicin sodium are summarised in Table 4.

| Property                                      | Value                  | Unit |
|-----------------------------------------------|------------------------|------|
| Molecular weight                              | 895                    | g/mol|
| Octanol/water partition coefficient (log $K_{ow}$) | 4.49 at pH 4          | –    |
|                                              | 2.63 at pH 7           | –    |
|                                              | 2.21 at pH 9           | –    |
| Solubility at 20°C                            | Milli-Ro water 1.39    | g/L  |
|                                              | pH 4 buffer 0.163      | –    |
|                                              | pH 7 buffer 1.24       | –    |
|                                              | pH 9 buffer 1.02       | –    |
| Dissociation constant pKa                      | 5.39                   | –    |
| Vapour pressure                               | $6.67 \times 10^{-28}$ | Pa   |

### Fate and behaviour

#### Fate in soil

**Adsorption**

No new studies were submitted. The two studies, already evaluated by the FEEDAP Panel in 2018 (EFSA FEEDAP Panel, 2018b), were re-evaluated for the present assessment. The FEEDAP Panel updated its previous evaluation as follows.

In the first study, originally performed on four soils, about 20% of the samples were lost (due to broken centrifuge glass tubes), leaving sufficient evidence for three soils. The method used (in accordance with Food and Drug Administration (FDA) and OECD guidelines which were in force at the time the study was conducted) can be accepted; all tests were performed at pH higher than 5.4, where degradation may occur. Glass tubes contained 40–44 mL of water and 2.2–8 g of soil. Adsorption to vessel apparently did not occur, with adsorption coefficient ($K_{oc}$) resulting the same either soil adsorption is considered or not. The $K_{oc}$ ranges recalculated are reported in Table 5.

#### Table 5: Recalculated $K_{oc}$ ranges in the adsorption study

| Soil               | $K_{oc}$ range mL/g | Solution to soil ratio |
|--------------------|---------------------|------------------------|
| Silty clay loam    | 1,400–2,100         | 20 to 1                |
| Silty loam         | 950–1,520           | 20 to 1                |
| Sandy loam         | 120–180             | 5 to 1                 |

$K_{oc}$: adsorption or desorption coefficient corrected for soil organic carbon content.

The FEEDAP Panel noted that the reliability of the results of the second study is highly questionable and this study cannot be used for the assessment for a number of reasons: the mass balance is described to be as low as 50%, and this is totally attributed to container adsorption; despite suspects on container adsorption, 50-mL centrifuge teflon tubes were filled to only < 20% (5 mL of water and 5 g of soil); an indirect method is claimed to account for adsorption on container, but radioactivity in the soil pellets (5 g) was determined by combustion analysis of only 0.1 g aliquots (2% of 2 mm sieved soil which corresponds to less than 10 sand grains); several editorial mistakes were identified in the text.

---

13 Technical dossier/Supplementary information January 2021/Attachment_2.
14 FAD-2015-0037 Technical dossier/Section III/Annex III_66.
15 FAD-2015-0037 Technical dossier/Section III/Annex III_65.
16 Calculated using the estimation software Epi-Suite.
17 FAD-2015-0037 Technical dossier/Section III/Annex 67.
18 FAD-2015-0037 Technical dossier/Section III/Annex 68.
Considering that just three \( K_{oc} \) values from the first study can be considered acceptable, the FEEDAP Panel agrees that the lowest one \( (K_{oc} \ 150 \text{ mL/g according Freundlich kinetics with a coefficient value of 0.82}) \) will be considered as the reference value for further PEC calculations.

**Degradation**

The degradation of \([^{14}C]\)-semduramicin sodium was investigated in a GLP-compliant study, in accordance with OECD Guideline 307.\(^{19}\) The FEEDAP Panel re-evaluated this study and agrees that the assessment done in the opinion adopted in 2018 (EFSA FEEDAP Panel, 2018b) is applicable to the current assessment. The main results of the studies are reported in Table 6.

The \( DT_{50} \) and \( DT_{90} \) values were estimated using a single first-order kinetic model; the geometric mean at 20\(^\circ\)C were 65 days and 216 days, respectively.

**Table 6:** Half-life \((DT_{50} \text{ and } DT_{90})\) of semduramicin in different soils at 20 and 12\(^\circ\)C

| Soil                | \( DT_{50} \) at 12\(^\circ\)C (days) | \( DT_{50} \) at 20\(^\circ\)C (days) | \( DT_{90} \) at 12\(^\circ\)C (days) | \( DT_{90} \) at 20\(^\circ\)C (days) |
|--------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Neutral sandy loam | 158                                 | 74                                  | 519                                 | 244                                 |
| Acidic sandy loam  | 168                                 | 79                                  | 558                                 | 262                                 |
| Silt loam          | 140                                 | 66                                  | 466                                 | 219                                 |
| Clay loam          | 100                                 | 47                                  | 332                                 | 156                                 |
| Arithmetic mean    | 140                                 | 66                                  | 469                                 | 220                                 |
| Geometric mean     | 138                                 | 65                                  | 460                                 | 216                                 |

\( DT_{50}: \text{time to degradation of 50}\% \text{ of original concentration of the compound in the tested soils; } DT_{90}: \text{time to degradation of 90}\% \text{ of original concentration of the compound in the tested soils.} \)

When the soil \( DT_{50} \) and \( DT_{90} \) are adjusted to a temperature of 12\(^\circ\)C (EFSA FEEDAP Panel, 2019), the geometric mean of \( DT_{50} \) and \( DT_{90} \) is 138 days and 460 days, respectively. These values are used for further calculations.

**Conclusion on fate and behaviour**

A \( K_{oc} \) of 150 \text{ mL/g} and a \( DT_{50} \) for transformation of semduramicin of 138 days at 12\(^\circ\)C are used for further calculations. Semduramicin sodium is considered to be hydrolytically stable.

**Predicted environmental concentrations**

The predicted environmental concentrations (PECs) were calculated according to the FEEDAP technical guidance for assessing the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019). The input values used for initial PEC calculations were: semduramicin sodium dose of 25 mg/kg feed, molecular weight of 895 g/mol, vapour pressure of \( 6.67 \times 10^{-28} \text{ Pa} \), solubility of 1,240 mg/L, \( DT_{50} \) of 138 days (at 12\(^\circ\)C) and \( K_{oc} \) of 150 L/kg. The PEC values are reported in Table 7.

**Table 7:** Initial predicted environmental concentrations (PECs) of semduramicin in soil (\( \mu g/\text{kg} \)) and groundwater (\( \mu g/\text{L} \))

| Compartment   | PEC |
|---------------|-----|
| Soil          | 378 |
| Ground water  | 30  |

The Phase I trigger values were exceeded. Therefore, a Phase II assessment is considered necessary.

**3.2.4.2. Phase II**

**Exposure assessment**

PEC calculation refined in Phase II

**Refinement based on metabolism**

For the refinement of the PECs based on the metabolism, the FEEDAP Panel agreed to follow the approach that was already used in its previous evaluation (EFSA FEEDAP Panel, 2018b) in which the

---

\(^{19}\) FAD-2015-0037 Technical dossier/Section III/Annex 71.
dose of semduramicin can be refined based on 33% of the residual ionophoric activity of semduramicin and its active metabolite; a dose of $25 \times 0.33 = 8.25$ mg/kg feed is used for further refinement calculation.

**Refinement of PECs for persistent compounds**

According to EFSA guidance (EFSA FEEDAP Panel, 2019), if a high persistence in soil is anticipated (DT$_{90} > 1$ year), the potential for residues to accumulate in soil should be considered. This is the case for semduramicin.

The re-calculated PECs values, refined for metabolism and persistence, are given in Table 8.

**Table 8:** Predicted environmental concentrations of semduramicin sodium in soil ($\mu$g/kg), groundwater ($\mu$g/L), surface water ($\mu$g/L) and sediment ($\mu$g/kg) refined for metabolism and persistent compounds

| Compartment       | PEC  |
|-------------------|------|
| Soil              | 148  |
| Ground water      | 12   |
| Surface water     | 3.9  |
| Sediment          | 73   |

PEC: predicted environmental concentration.

**PEC$_{\text{groundwater refined with FOCUS}}$**

To address the leaching of semduramicin to groundwater, the applicant provided calculation with FOCUS PEARL 5.5.5 according to the EFSA guidance (EFSA FEEDAP Panel, 2019). The application rate considered was 0.094 kg/ha, derived from the PEC$_{\text{soil}}$ refined for metabolism. The other input data were a DT$_{50}$ at 20°C of 65 days and a K$_{oc}$ of 150 L/kg (recalculated in an organic matter/water distribution coefficient (K$_{om}$) of 87 L/kg) with a Freundlich exponent of 0.82. The type of application considered was the incorporation into soil (depth of 20 cm) in the two scenarios for poultry indicated in the aforementioned guidance. The 80th percentile annual average recharge concentrations leaving the top 1 m soil layer for a 20-year period are reported in the Table 9.

**Table 9:** Predicted environmental concentration in groundwater at 1 m depth following the use of semduramicin sodium in chickens for fattening

| Application rate (kg/ha) | FOCUS scenario | PEC$_{gw}$ ($\mu$g/L)  |
|--------------------------|----------------|------------------------|
| 0.094 Jokioinen          | 0.003          |
| 0.094 Piacenza           | 0.016          |

PEC: predicted environmental concentration.

The PEC$_{gw}$ values for both scenarios are below the trigger value of 0.1 $\mu$g/L when using soil incorporation (worst-case). Therefore, it can be concluded that no concern is expected for groundwater when the additive is used at the maximum proposed dose.

**Conclusions on PECs used for calculation**

The following values are used for the assessment: a PEC$_{\text{soil}}$ refined for metabolism and persistence of 148 $\mu$g/kg, a PEC$_{\text{surface water}}$ of 3.9 $\mu$g/L and a PEC$_{\text{sediment}}$ of 73 $\mu$g/kg.

**Ecotoxicity studies**

Toxicity to terrestrial compartment

The effects of semduramicin sodium on terrestrial plants, earthworm and on soil nitrogen transformations were investigated in studies already evaluated by the previous FEEDAP opinion (EFSA FEEDAP Panel, 2018b).
The FEEDAP Panel checked the updated report of the plant study submitted for the current assessment and confirmed that the relevant endpoint for the assessment of the toxicity to plant is the lowest EC10 of 1.3 mg/kg dry soil for shoot weight in tomatoes. The FEEDAP Panel also confirmed that the incorporation of semduramicin sodium into soil had no prolonged effect on soil nitrogen transformations.

In 2018, the acute no observed effect concentration (NOEC) of 10 mg/kg for mortality and growth was derived from the available earthworm study (EFSA FEEDAP Panel, 2018b). This study was re-evaluated for the current assessment, and it was noted that since it is an acute one, the only relevant endpoint is the mortality. Therefore, the FEEDAP Panel considered appropriate to use the calculated LC50 of 526 mg/kg for the assessment of the risk characterisation instead of the NOEC of 10 mg/kg used in its previous evaluation.

Toxicity to aquatic organisms

Effect on algae, crustaceans and fish

The effect of semduramicin sodium to the algal species Raphidocelis subcapitata (former names: Selenastrum capricornutum, Pseudokirchneriella subcapitata) was investigated in a newly performed GLP-compliant study, in accordance with the OECD guidelines 201. A 4-day-old culture of the algae in the exponential growth phase was used as inoculum for the test. The culture was grown in the medium under the environmental conditions described for the test. Algae were exposed over a 72-h period to nominal semduramicin sodium concentrations of 0.954, 3.05, 9.77, 31.3 and 100 mg/L. A corresponding control was also included in the study. Exposure concentrations were measured by liquid chromatography tandem mass spectrometry (LC–MS/MS) and were maintained over the 72-h exposure period. At 0 h, measured concentrations of semduramicin sodium were 94–108% of nominal and the corresponding range at 72 h was 87–103%. As such, results were expressed with respect to mean nominal concentrations. The test was considered valid since all the validity criteria were fulfilled.

Under the conditions described above, the ErC50 value for semduramicin sodium was 33.5 mg/L.

For the current assessment the applicant made reference to the studies on the effects on crustaceans and fish already evaluated (EFSA FEEDAP Panel, 2018b). These studies were re-evaluated, and the same conclusions are considered valid for the current assessment; the following values are used for the risk characterisation: the EC50 of 38 mg/L and 32 mg/L for crustaceans and fish, respectively.

Additional information on aquatic toxicity

A growth inhibition test of Anabaena floaquae according to OECD Guideline 201 and acute toxicity test with bluegill (Lepomis macrochirus) under static conditions investigated in accordance with ASTM Standard E729-80 were submitted. The FEEDAP Panel confirms that the 72-h EC50 for growth in the test with Anabaena floaquae is 66 mg/L and that the LC50 value for semduramicin sodium in the test with bluegill is 38 mg/L, equivalent to 37 mg/L (EFSA FEEDAP Panel, 2018b).

Effect on sediment dwelling organisms

For the current assessment, the applicant made reference to the study on the effects on sediment dwelling organism already evaluated by the FEEDAP Panel in 2018 (EFSA FEEDAP Panel, 2018b). The FEEDAP Panel confirmed that the EC10 of 102 mg semduramicin sodium/kg dry weight can be used for the risk characterisation.

Risk characterisation (PEC/PNEC ratio)

For the terrestrial compartment, data are available for micro-organisms, earthworms and plants. The risk for terrestrial compartment was evaluated based on a plant study resulting in the lowest EC10 value of 1.3 mg/kg. For the aquatic compartment, data are available for algae, aquatic invertebrates and fish. The lowest acute toxicity value of 32 mg/L for the aquatic compartment was found in a study on the effect on fish. Ecotoxicological data for sediment-dwelling invertebrate Chironomus riparius were provided for the sediment compartment resulting in an EC10 of 102 mg/kg.

The risk characterisation ratios for terrestrial, freshwater and sediment compartments are reported in Tables 10, 11, 12.

---

24 Technical dossier/Supplementary information November 2021/Appendix 4 and Appendix 5a and 5b.
25 Technical dossier/Annex 5.
26 FAD-2015-0037 Technical dossier/Section III/Annex 77.
27 FAD-2015-0037 Technical dossier/Section III/Annex 79.
28 FAD-2015-0037 Technical dossier/Section III/Annex 81.
The risk characterisation ratios indicate that no risk is expected for aquatic and sediment compartments; a risk for the terrestrial compartment cannot be excluded.

Bioaccumulation and secondary poisoning

Since the log Kow of semduramicin is estimated as 2.63 at pH 7 (lower than the trigger value of 3), the bioaccumulation is considered to be low and the risk for secondary poisoning is not likely to occur.

3.2.4.3. Conclusions on safety for the environment

The use of semduramicin sodium from Aviax 5% in feed for chickens for fattening up to 25 mg/kg complete feed does not pose a risk for groundwater nor for aquatic and sediment compartments. A risk for the terrestrial compartment cannot be excluded. The bioaccumulation and the risk for secondary poisoning are considered to be low.

4. Conclusions

Based on the new data provided, the FEEDAP Panel concludes that there are no safety concerns for the target animal, consumer, user and environment regarding the production strain of semduramicin sodium.

Table 10: Risk characterisation (PEC/PNEC ratio) of semduramicin for terrestrial compartment

| Taxa                        | PECsoil (µg/kg) | LC50/EC10 (mg/kg) | AF | PNEC (µg/kg) | PEC/PNEC |
|-----------------------------|----------------|-------------------|----|--------------|----------|
| Earthworm\(^{(1)}\)         | 148            | 526               | 1,000| 526         | 0.2      |
| Plants\(^{(2)}\)            | 1.3            | 10                | 130 | 130         | 1.14     |

PEC: predicted environmental concentration; PNEC: predicted no effect concentration; LC50: the concentration of a test substance which results in a 50% mortality of the test species; EC10: the concentration of a test substance which results in 10% of the test organisms being adversely affected, i.e. both mortality and sublethal effects; AF: assessment factor.

\(^{(1)}\): PNEC derived from LC50.
\(^{(2)}\): PNEC derived from EC10.

Table 11: Risk characterisation (PEC/PNEC ratio) of semduramicin for freshwater compartment

| Taxa                        | PECsurfacewater (µg/L) | EC50/LC50 (mg/L) | AF | PNEC\(^{(4)}\) (µg/L) | PEC/PNEC |
|-----------------------------|-------------------------|-----------------|----|-----------------------|----------|
| Algae\(^{(1)}\) Raphidocelis subcapitata | 3.9                     | 33.5            | 1,000| 32         | 0.12     |
| Aquatic invertebrates\(^{(2)}\) Daphnia magna | 38                      |                 |     |                       |          |
| Fish\(^{(3)}\) Danio rerio | 32                      |                 |     |                       |          |

PEC: predicted environmental concentration; PNEC: predicted no effect concentration; ErC50: the concentration of a test substance which results in a 50% of inhibition of algal growth rate; LC50: the concentration of a test substance which results in a 50% mortality of the test species; AF: assessment factor.

\(^{(1)}\): ErC50.
\(^{(2)}\): LC50.
\(^{(3)}\): LC50.
\(^{(4)}\): PNEC derived from fish.

Table 12: Risk characterisation (PEC/PNEC ratio) of semduramicin for sediment

| Taxa                        | PECsediment (µg/kg) | EC10 (mg/kg) | AF | PNEC (µg/kg) | PEC/PNEC |
|-----------------------------|---------------------|--------------|----|--------------|----------|
| Sediment-dwelling invertebrates Chironomus riparius | 73                  | 102          | 100| 1,020        | 0.07     |

PEC: predicted environmental concentration; EC10: the concentration of a test substance which results in 10% of the test organisms being adversely affected, i.e. both mortality and sublethal effects; AF: assessment factor; PNEC: predicted no effect concentration.

The risk characterisation ratios indicate that no risk is expected for aquatic and sediment compartments; a risk for the terrestrial compartment cannot be excluded.
Based on the results in the tolerance trial, the FEEDAP Panel concludes that the additive is safe for chickens for fattening up to the maximum recommended level (25 mg/kg complete feed), but no margin of safety can be established.

The use of semduramicin sodium at a maximum level of 25 mg/kg complete feed for chickens for fattening is safe for consumers with no withdrawal time.

Based on the new data provided and the current requirements for the risk assessment of the environment, the use of semduramicin sodium from Aviax 5% in feed for chickens for fattening up to 25 mg/kg complete feed does not pose a risk for groundwater nor for aquatic and sediment compartments, while risk for the terrestrial compartment cannot be excluded. The bioaccumulation and the risk for secondary poisoning are considered to be low.

5. Documentation as provided to EFSA/chronology

| Date       | Event                                                                                           |
|------------|-------------------------------------------------------------------------------------------------|
| 13/11/2019 | Dossier received by EFSA. Additional data on Aviax 5% (semduramicin sodium) for chickens for fattening submitted by Phibro Animal Health s.a. |
| 13/12/2019 | Reception mandate from the European Commission                                                   |
| 07/01/2020 | Acceptance of the mandate by EFSA – Start of the scientific assessment.                           |
| 06/04/2020 | Request of supplementary information to the applicant in line with Article 7(3) of Commission Regulation (EC) No 1304/2003 – Scientific assessment suspended. Issues: Characterisation and Target animal safety |
| 28/07/2020 | Reception of supplementary information from the applicant - Scientific assessment re-started       |
| 29/09/2020 | Request of supplementary information to the applicant in line with Article 7(3) of Commission Regulation (EC) No 1304/2003 – Scientific assessment suspended. Issues: Characterisation, Methods of analysis, Consumer safety and Environmental safety |
| 07/01/2021 | Reception of supplementary information from the applicant                                         |
| 22/01/2021 | Reception of letter from European Union Reference Laboratory for Feed Additives confirming that no amendment to the former evaluation report is considered necessary - Scientific assessment re-started |
| 19/07/2021 | Request of supplementary information to the applicant in line with Article 7(3) of Commission Regulation (EC) No 1304/2003 – Scientific assessment suspended. Issues: Characterisation and Environmental safety |
| 19/11/2021 | Reception of supplementary information from the applicant - Scientific assessment re-started       |
| 29/06/2022 | Opinion adopted by the FEEDAP Panel. End of the Scientific assessment                             |

References

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2008. Technical Guidance for assessing the safety of feed additives for the environment. EFSA Journal 2008;842, 28 pp. https://doi.org/10.2903/j.efsa.2008.842

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, Lopez-Alonso M, Lopez Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Anguita M, Galobart J, Innocenti ML and Martino L, 2017a. Guidance on the assessment of the safety of feed additives for the target species. EFSA Journal 2017;15(10):5021, 19 pp. https://doi.org/10.2903/j.efsa.2017.5021

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, Lopez-Alonso M, Lopez Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Anguita M, Dujardin B, Galobart J and Innocenti ML, 2017b. Guidance on the assessment of the safety of feed additives for the consumer. EFSA Journal 2017;15(10):5022, 17 pp. https://doi.org/10.2903/j.efsa.2017.5022

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, Lopez-Alonso M, Lopez Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Glendorf B, Herman L, Kärenlampi S, Aguiera J, Anguita M, Brozzi R and Galobart J, 2018a. Guidance on the characterisation of microorganisms used as feed additives or as production organisms. EFSA Journal 2018;16(3):5206, 24 pp. https://doi.org/10.2903/j.efsa.2018.5206
EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Kolar B, Kouba M, López-Alonso M, López Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Brantom P, Halle I, van Beelen P, Holczknecht O, Vettori MV and Gropp J, 2018b. Scientific Opinion on the safety and efficacy of Aviax 5% (semduramicin sodium) for chickens for fattening. EFSA Journal 2018;16(7):5341, 42 pp. https://doi.org/10.2903/j.efsa.2018.5341

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Bampidis V, Bastos ML, Christensen H, Dusemund B, Kouba M, Kos Durjava M, López-Alonso M, López Puente S, Marcon F, Mayo B, Pachová A, Petkova M, Ramos F, Sanz Y, Villa RE, Woutersen R, Brock T, Knecht J, Kolar B, Beelen P, Padovani L, Tarrés-Call J, Vettori MV and Azimonti G, 2019. Guidance on the assessment of the safety of feed additives for the environment. EFSA Journal 2019;17(4):5648, 78 pp. https://doi.org/10.2903/j.efsa.2019.5648

Wieme AD, Gosselée F, Snauwaert C, Cleenwerck I and Vandamme P, 2019. Actinomadura roseirufa sp. nov., producer of semduramicin, a polyether ionophore. International Journal Of Systematic And Evolutionary Microbiology, 69, 3068–3073. https://doi.org/10.1099/ijsem.0.003591

**Abbreviations**

| Term            | Definition                                                                 |
|-----------------|-----------------------------------------------------------------------------|
| ADI             | acceptable daily intake                                                    |
| AF              | assessment factor                                                           |
| ATCC            | American Type Culture Collection                                             |
| bw              | Body weight                                                                 |
| DT$_{50}$       | time to degradation of 50% of original concentration of the compound in the tested soils |
| DT$_{90}$       | time to degradation of 90% of original concentration of the compound in the tested soils |
| EC$_{10}$       | the concentration of a test substance which results in 10% of the test organisms being adversely affected, i.e. both mortality and sublethal effects |
| EC$_{50}$       | the concentration of a test substance which results in 50% of the test organisms being adversely affected, i.e. both mortality and sublethal effects |
| ErC$_{50}$      | the concentration of a test substance which results in a 50% of inhibition of algal growth rate |
| FDA             | Food and Drug Administration                                                |
| FEEDAP          | EFSA Panel on Additives and Products or Substances used in Animal Feed      |
| FOCUS           | Forum for Co-ordination of pesticide models and their Use                   |
| GLP             | Good Laboratory Practices                                                   |
| K$_{OC}$        | adsorption or desorption coefficient corrected for soil organic carbon content |
| K$_{OM}$        | organic matter/water distribution coefficient                               |
| LC–MS/MS        | liquid chromatography with tandem mass spectrometry                         |
| LC$_{50}$       | the concentration of a test substance which results in a 50% mortality of the test species |
| log K$_{OW}$    | n-octanol/water partition coefficient                                        |
| MRL             | maximum residue limit                                                       |
| NOEC            | no observed effect concentration                                            |
| OECD            | Organisation for Economic Co-operation and Development                      |
| PEC             | predicted environmental concentration                                        |
| PNEC            | predicted no effect concentration                                           |
| WGS             | whole genome sequence                                                       |

www.efsa.europa.eu/efsajournal 14 EFSA Journal 2022;20(8):7432
## Appendix A – Detailed results on chronic exposure calculation

### Table A.1: Chronic exposure of consumers to semduramicin-related total residues based on residue data measured in chicken tissues at 6 h withdrawal time

| Population class | Survey’s country | Number of subjects | Highest exposure estimate (µg/kg bw per day) | HRP description |
|------------------|------------------|--------------------|---------------------------------------------|-----------------|
| Infants          | Bulgaria         | 523                | 0.2458                                      | 95th            |
| Infants          | Germany          | 142                | 0.0447                                      | 95th            |
| Infants          | Denmark          | 799                | 0.0519                                      | 95th            |
| Infants          | Finland          | 427                | 0.0776                                      | 95th            |
| Infants          | Italy            | 9                  | 0.0000                                      | 50th            |
| Infants          | United Kingdom   | 1,251              | 0.1096                                      | 95th            |
| Toddlers         | Belgium          | 36                 | 0.1144                                      | 90th            |
| Toddlers         | Bulgaria         | 428                | 0.4387                                      | 95th            |
| Toddlers         | Germany          | 348                | 0.0754                                      | 95th            |
| Toddlers         | Denmark          | 917                | 0.0576                                      | 95th            |
| Toddlers         | Spain            | 17                 | 0.1122                                      | 75th            |
| Toddlers         | Finland          | 500                | 0.1239                                      | 95th            |
| Toddlers         | Italy            | 36                 | 0.1022                                      | 90th            |
| Toddlers         | Netherlands      | 322                | 0.1256                                      | 95th            |
| Toddlers         | United Kingdom   | 1,314              | 0.1195                                      | 95th            |
| Toddlers         | United Kingdom   | 185                | 0.1254                                      | 95th            |
| Other children   | Austria          | 128                | 0.0991                                      | 95th            |
| Other children   | Belgium          | 625                | 0.1426                                      | 95th            |
| Other children   | Bulgaria         | 433                | 0.6047                                      | 95th            |
| Other children   | Germany          | 293                | 0.0905                                      | 95th            |
| Other children   | Germany          | 835                | 0.0788                                      | 95th            |
| Other children   | Denmark          | 298                | 0.0644                                      | 95th            |
| Other children   | Spain            | 399                | 0.1457                                      | 95th            |
| Other children   | Spain            | 156                | 0.2040                                      | 95th            |
| Other children   | Finland          | 750                | 0.2109                                      | 95th            |
| Other children   | France           | 482                | 0.1995                                      | 95th            |
| Other children   | Greece           | 838                | 0.1043                                      | 95th            |
| Other children   | Italy            | 193                | 0.1099                                      | 95th            |
| Other children   | Latvia           | 187                | 0.1184                                      | 95th            |
| Other children   | Netherlands      | 957                | 0.0916                                      | 95th            |
| Other children   | Netherlands      | 447                | 0.1153                                      | 95th            |
| Other children   | Sweden           | 1,473              | 0.0864                                      | 95th            |
| Other children   | Czechia          | 389                | 0.2158                                      | 95th            |
| Other children   | United Kingdom   | 651                | 0.1065                                      | 95th            |
| Adolescents      | Austria          | 237                | 0.0685                                      | 95th            |
| Adolescents      | Belgium          | 576                | 0.0627                                      | 95th            |
| Adolescents      | Cyprus           | 303                | 0.0662                                      | 95th            |
| Adolescents      | Germany          | 393                | 0.0607                                      | 95th            |
| Adolescents      | Germany          | 1,011              | 0.0501                                      | 95th            |
| Adolescents      | Denmark          | 377                | 0.0503                                      | 95th            |
| Adolescents      | Spain            | 651                | 0.0846                                      | 95th            |
| Adolescents      | Spain            | 209                | 0.1136                                      | 95th            |
| Adolescents      | Spain            | 86                 | 0.1166                                      | 95th            |

Dietary data from the UK were included in FACE when the UK was a member of the European Union.
| Population class | Survey’s country | Number of subjects | Highest exposure estimate (μg/kg bw per day) | HRP description |
|------------------|------------------|--------------------|---------------------------------------------|-----------------|
| Adolescents      | Finland          | 306                | 0.0635                                      | 95th            |
| Adolescents      | France           | 973                | 0.1205                                      | 95th            |
| Adolescents      | Italy            | 247                | 0.0505                                      | 95th            |
| Adolescents      | Latvia           | 453                | 0.0721                                      | 95th            |
| Adolescents      | Netherlands      | 1,142              | 0.0865                                      | 95th            |
| Adolescents      | Sweden           | 1,018              | 0.0651                                      | 95th            |
| Adolescents      | Czechia          | 298                | 0.1633                                      | 95th            |
| Adolescents      | United Kingdom   | 666                | 0.0781                                      | 95th            |
| Adults           | Austria          | 308                | 0.0784                                      | 95th            |
| Adults           | Belgium          | 1,292              | 0.0671                                      | 95th            |
| Adults           | Germany          | 10,419             | 0.0506                                      | 95th            |
| Adults           | Denmark          | 1,739              | 0.0328                                      | 95th            |
| Adults           | Spain            | 981                | 0.0814                                      | 95th            |
| Adults           | Spain            | 410                | 0.0789                                      | 95th            |
| Adults           | Finland          | 1,295              | 0.0651                                      | 95th            |
| Adults           | France           | 2,276              | 0.1028                                      | 95th            |
| Adults           | Hungary          | 1,074              | 0.1420                                      | 95th            |
| Adults           | Ireland          | 1,274              | 0.0778                                      | 95th            |
| Adults           | Italy            | 2,313              | 0.0433                                      | 95th            |
| Adults           | Latvia           | 1,271              | 0.0649                                      | 95th            |
| Adults           | Netherlands      | 2,055              | 0.0729                                      | 95th            |
| Adults           | Romania          | 1,254              | 0.5279                                      | 95th            |
| Adults           | Sweden           | 1,430              | 0.0669                                      | 95th            |
| Adults           | Czechia          | 1,666              | 0.0854                                      | 95th            |
| Adults           | United Kingdom   | 1,265              | 0.0577                                      | 95th            |
| Elderly          | Austria          | 67                 | 0.0691                                      | 95th            |
| Elderly          | Belgium          | 511                | 0.0573                                      | 95th            |
| Elderly          | Germany          | 2,006              | 0.0404                                      | 95th            |
| Elderly          | Denmark          | 274                | 0.0265                                      | 95th            |
| Elderly          | Finland          | 413                | 0.0562                                      | 95th            |
| Elderly          | France           | 264                | 0.0919                                      | 95th            |
| Elderly          | Hungary          | 206                | 0.0853                                      | 95th            |
| Elderly          | Ireland          | 149                | 0.0645                                      | 95th            |
| Elderly          | Italy            | 289                | 0.0504                                      | 95th            |
| Elderly          | Netherlands      | 173                | 0.0541                                      | 95th            |
| Elderly          | Netherlands      | 289                | 0.0460                                      | 95th            |
| Elderly          | Romania          | 83                 | 0.0985                                      | 95th            |
| Elderly          | Sweden           | 295                | 0.0635                                      | 95th            |
| Elderly          | United Kingdom   | 166                | 0.0494                                      | 95th            |
| Very elderly     | Austria          | 25                 | 0.0165                                      | 75th            |
| Very elderly     | Belgium          | 704                | 0.0635                                      | 95th            |
| Very elderly     | Germany          | 490                | 0.0415                                      | 95th            |
| Very elderly     | Denmark          | 12                 | 0.0139                                      | 75th            |
| Very elderly     | France           | 84                 | 0.0610                                      | 95th            |
| Very elderly     | Hungary          | 80                 | 0.0641                                      | 95th            |
| Very elderly     | Ireland          | 77                 | 0.0644                                      | 95th            |
| Very elderly     | Italy            | 228                | 0.0426                                      | 95th            |
| Very elderly     | Netherlands      | 450                | 0.0456                                      | 95th            |
| Population class | Survey’s country | Number of subjects | Highest exposure estimate (µg/kg bw per day) | HRP description |
|------------------|------------------|--------------------|-----------------------------------------------|-----------------|
| Very elderly     | Romania          | 45                 | 0.2232                                        | 90th            |
| Very elderly     | Sweden           | 72                 | 0.0472                                        | 95th            |
| Very elderly     | United Kingdom   | 139                | 0.0356                                        | 95th            |