REGULATED PRODUCTS SAFETY ASSESSMENT

Assessment on the Safety and Efficacy of Modification of the Terms of Authorisation of zinc-L-selenomethionine as a Feed Additive for All Animal Species (Zinpro Animal Nutrition (Europe), Inc.) (RP1823)

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FSA Research and Evidence

An application was submitted to the Food Standards Agency in November 2022 from Zinpro Animal Nutrition (Europe), Inc. ("the applicant") for the modification to the authorisation of an additive consisting of zinc-L-selenomethionine, under the category of 'nutritional additive' and functional group 'compounds of trace elements' for its use in all animal species as source of selenium (Se) with a content of 4%.

Under its current authorisation (Commission Implementing Regulation (EU) 2019/49) the additive is described as "Solid preparation of zinc-L-selenomethionine with a selenium content of 1-2 g/kg". The applicant developed a new formula for the additive containing a minimum of 40 g Se/kg. Therefore, the modification to the current authorisation is sought and a wider specification for the Se content of 1-46 g/kg is requested.

EFSA's FEEDAP Panel concluded that the newly proposed preparation of zinc-L-selenomethionine is considered safe for all animals, consumers and the environment. However, the Panel recommended adding to the current authorisation a new preparation of 40-46 g Se/kg as no characterisation data has been provided on the preparation range of 2-40 g Se/kg. The modification has no impact on efficacy according to the FEEDAP Panel.

The newly proposed preparation of the additive presents a risk by inhalation, but it is not irritant to skin or eyes. Conclusions could not be drawn on the potential to cause dermal sensitisation.

FSA/FSS has reviewed the applicant's modification to the authorisation application, supporting documentation, and other regulators risk assessments, most notably the EFSA risk assessment opinion and considers that sufficient evidence has been demonstrated to conclude without the need for further questions or risk assessment.

This is a joint FSA and FSS publication

1. Introduction

The FSA and FSS have undertaken an assessment of a feed additive (Zinpro Animal Nutrition (Europe), Inc, Akkerdistel 2E, 5831 PJ, Boxmeer, Netherlands) consisting of zinc-L-selenomethionine under Assimilated Regulation (EC) No 1831/2003 (EC, 2003) in each nation of Great Britain (GB) for a modification to current authorisation under category of 'nutritional additive' and functional group 'compounds of trace elements' for its use in all animal species as source of selenium (Se) from a content of 0.1% to a content of 4% Se.

In line with Article 8 of Assimilated Regulation No 1831/2003, the assessment has considered and concluded that the feed additive complies with the conditions laid down in Article 5, including: safety considerations for human, animal and environmental health; efficacy of the additive for its intended effect; potential impairment of the distinctive features of animal products. This, and the guidance put in place by the European Food Safety Authority (EFSA) for the evaluation of feed additive applications, has formed the basis and structure for the assessment.

To ensure regulatory systems of FSA/FSS are risk proportionate and resources are used effectively, FSA and FSS have used the evidence submitted by the applicant and other information in the public domain, including the EFSA risk assessment opinion, to provide a summary assessment of the evidence of safety presented in this report.

In 2023, EFSA published a risk assessment opinion on the modification of the terms of authorisation of zinc-L-selenomethionine as a feed additive for all animal species submitted by Zinpro Animal Nutrition (Europe), Inc. This opinion and the previous opinion published in 2018 have been reviewed by FSA/FSS risk assessors. It has been verified that the standard approach taken, when compared to the relevant guidance applied in GB, has been followed and the conclusions made are consistent with the data summarised in the opinion.

The result of the assessment is that there is sufficient evidence of safety for the UK to conclude this assessment at this time. This assessment represents the opinion of the FSA and FSS.

Table 1. Table showing products included in this assessment

Title	Product type	Intended use/s	Intended dose/intake
Zinc-l-selenomethionine	Feed additive	Nutritional additive	Maximum supplementation rate of 0.2 mg Se/kg feed not exceeding a total selenium concentration of 0.5 mg/kg feed

2. Assessment

2.1. Details of other regulators opinions

2.1.1. Current authorisation

Zinc-L-selenomethionine was authorised as a nutritional feed additive, compounds of trace elements, under Commission Implementing Regulation (EU) 2019/49 (EC, 2019), with the EU number 3b818. The current authorisation specifies the additive composition as a "solid preparation of zinc-L-selenomethionine with a selenium content of 1–2 g/kg." The applicant has now developed a new formula with a guaranteed minimum of 40 g selenium per kg and seeks a modification of the authorisation to allow a wider selenium content range: "solid preparation of zinc-L-selenomethionine with a selenium content of 1–46 g/kg."

2.1.2. Other regulators opinions

In 2018, FEEDAP Panel concluded, that zinc-L-selenomethionine (Zn-L-SeMet; a minimum of selenium and SeMet of 1,000 and 2,500 mg/additive, respectively) is a safe and effective source of selenium for chickens for fattening, with this conclusion extended to all animal species (EFSA, 2018b). Selenium from Zn-L-SeMet does not cause any adverse effects beyond those expected from a selenium compound, and its use in animal nutrition is expected to result in similar selenium deposition in tissues/products as other SeMet sources. It is safe for consumers if the maximum selenium supplementation level (0.2 mg/kg in complete feed) and the total authorised selenium content (0.5 mg/kg in complete feed) are respected.

The additive poses an inhalation hazard due to its high dusting potential, though it is not a skin irritant. No conclusions could be drawn on eye irritation or skin sensitization due to a lack of data at that time. Zn-L-SeMet does not pose additional environmental risks compared to other selenium sources, provided the maximum feed content is not exceeded. The zinc contribution from the additive (< 0.2 mg Zn/kg feed) is minimal and does not require further safety assessment, except for users.

The FEEDAP Panel recommended that the additive should be added to feed via premixture, ensuring homogeneous distribution.

In 2023, EFSA published a risk assessment opinion on the modification of the terms of authorisation of zinc-L-selenomethionine as a feed additive for all animal species.

2.1.3. Methodology applied in the EFSA opinions

The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) assessed the safety and the efficacy of a new preparation of zinc-L-selenomethionine, in accordance with guidance documents: Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEEDAP Panel, 2017c), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018a), Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel 2017a), Guidance for the preparation of dossiers for nutritional additives (EFSA FEEDAP Panel, 2012a), Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012b), Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019) and principles in Assimilated Regulation (EC) No 429/2008 (EC, 2008).

These guidance documents were developed and implemented prior to the UK's exit from the EU and were also adopted by FSA and FSS on exit.

2.2. Section II: Identity, characterisation and condition of use

2.2.1. Characterisation of the active substance and the additive

The active substance in the additive is (S)-2-amino-4-methylselanyl-butanoic acid zinc complex, also known as zinc-L-selenomethionine (Zn-L-SeMet), in chloride form, with the chemical formula $C_5H_{10}ClNO_2SeZn$ and a molecular weight of 295.94 g/mol. The current authorisation specifies the active substance as crystalline powder with L-selenomethionine > 62%, selenium > 24.5%, chloride > 20% and zinc > 19%. The current composition of the additive on the market contains 1–2 g Se/kg from the active substance zinc-L-selenomethionine, silicon dioxide (1.62%), vegetable oil (1.02%) and calcium carbonate (97%). The new preparation of the additive (Zn-L-SeMet-4%Se) proposes a minimum of 40 g Se/kg, obtained by mixing zinc-L-selenomethionine (14.4%) with silicon dioxide (E551) (85.6%). An analysis of five batches of Zn-L-SeMet-4%Se showed an average of 43.32

g/kg (range: 42.20–44.40 g/kg) of selenium, 36.32 g/kg (range: 34.40–38.20 g/kg) of zinc, and 111.86 g/kg (range: 102.30–117.00 g/kg) of L-selenomethionine.

The mycotoxin analysis of 3 batches, including aflatoxins (B1, G1, B2, G2) and ochratoxin A were all below 1 µg/kg. Furthermore, analysis of 3 batches of the additive demonstrated compliance with predefined specifications: *Salmonella spp.* (not detected in 25 g), yeasts and moulds (<10 CFU/g), and *Enterobacteriaceae* (<10 CFU/g). Testing of three batches showed arsenic (As) concentrations at 0.24 mg/kg (range: 0.12–0.36 mg/kg), cadmium (Cd) below 0.1 mg/kg, lead (Pb) at 0.49 mg/kg (range: 0.39–0.59 mg/kg), mercury (Hg) below 0.01 mg/kg, and fluoride ranging from 29 to 31 mg/kg. In addition, analysis of three batches showed average levels of dioxins at 0.15 ng WHO-PCDD/F-TEQ/kg, and the sum of dioxins plus dioxin-like PCBs at 0.20 ng WHO-PCDD/F-PCB-TEQ/kg (upper bound), while non-dioxin-like PCBs were at 0.02 µg/kg additive (upper bound).

The FEEDAP Panel concluded that the amounts of the detected impurities as well as microbial contamination, do not raise safety concerns.

The applicant stated that the manufacturing process of the active compound, which involves complexing L-selenomethionine (L-SeMet; from chemical synthesis) with zinc to form the Zn-L-SeMet complex, has not been modified since the previous EFSA opinion (EFSA, 2018b).

Zn-L-SeMet-4%Se is a blue powder with a bulk density of 562 kg/m^3 (range 555–570 kg/m3). Using the Stauber-Heubach method on three batches of additive, an average of dusting potential of 2308 mg/m^3 (range 2284–2344 mg/m^3) was determined. A laser diffraction showed that on average, 83.3% (v/v) of the dust particles were below the size of 10 µm and 9.6% (v/v) were below 1 µm. Zinc and selenium were not found in the dust. The laser diffraction analysis of the additive showed that on average 6.2% (v/v) of the particles were below 100 µm, 3.93% (v/v) were below 50 µm and 1.23% (v/v) were below 10 µm.

No new data on stability were provided by the applicant. Ten samples were analysed to study the homogeneity of the distribution of the additive, showing an average selenium content of 341 mg Se/kg in the mineral premix, 55.3 mg Se/kg in the starter premix, and 52.4 mg Se/kg in the grower premix, with the coefficient of variation (CV) at 3.5%, 3.77%, and 4.23%, respectively. The average selenium content in the starter and grower mash feed was 0.187 mg Se/kg and 0.209 mg Se/kg, respectively, while in the pelleted feed, it was 0.193 mg Se/kg. The corresponding CVs were 3.7%, 5.8%, and 5.0%.

No changes to conditions of use for the new preparation were proposed. The additive should be incorporated to the feed via premixture and should be used up to a maximum supplementation rate of 0.2 mg Se/kg feed, not exceeding a total selenium concentration of 0.5 mg/kg feed.

The FSA/FSS agree with the view that there are no causes for concern in the identification and manufacturing process sections of the application. The additive has a high dusting potential and has a high percentage of small-sized particles. This should be taken into consideration to limit inhalation exposure. FSA/FSS agree that previous conclusions on stability apply to this application.

2.2.2. Conclusion on Section II

It was stated by the applicant that the manufacturing process was not modified since the previous EFSA opinion (EFSA, 2018b). An average content of the selenium 43.32 g Se/kg has been confirmed by analysis of 5 batches of the additive. Microbiological contamination analysis of 3 batches of the additive demonstrated compliance with predefined specifications. The FEEDAP Panel concluded that the amounts of the detected impurities as well as microbial contamination, do not raise safety concerns.

The FSA/FSS agree with the view that there are no causes for concern in the identification and manufacturing process sections of the application. The additive has a high dusting potential and has a high percentage of small-sized particles. This should be taken into consideration to limit inhalation exposure. FSA/FSS agree that previous conclusions on stability apply to this application.

2.3. Section III: Safety

2.3.1. Safety for the consumer and the environment

The FEEDAP Panel concluded that the proposed change to the authorisation terms, involving a higher selenium concentration in the additive, would not affect consumer or environmental safety, as the usage conditions adhere to the current maximum supplementation limits for selenium from all organic sources (0.2 mg/kg in complete feed). The same conclusion applies to zinc.

The FSA and FSS agree with the view that the additive is safe to consumers and the environment, despite the proposed changes in composition.

2.3.2. Safety for the target species

In the previous EFSA opinion (EFSA, 2018b), the FEEDAP Panel concluded that no adverse effects were observed in the zootechnical endpoints for the additive Zn- L-SeMet (a minimum of selenium and SeMet of 1,000 and 2,500 mg/kg additive, respectively) under assessment compared to both the already authorised inorganic sodium selenite and the unsupplemented control diet in a tolerance study in chickens for fattening. In addition, no adverse effects were observed in most haematology and serum biochemistry parameters. The few exceptions were statistically significant differences, which, if treatment-related, were of unclear biological relevance. Selenium bioavailability was indicated by the response of selenium serum levels and GPx activity to dietary Zn- L-SeMet. Therefore, it was concluded that Zn-L-SeMet is a safe source of selenium for chickens for fattening, and this conclusion was extended to all animal species.

The homogeneity study showed homogeneous distribution of the additive in the complete feed. Under the current conditions of use, the exposure of target animals to organic selenium is not expected to be affected by the product with a higher selenium concentration. In conclusion, the FEEDAP Panel considers the proposed increase in selenium concentration in the additive to be safe for all animal species.

The FSA and FSS agree with the view that the additive is safe to the target species, despite the proposed changes in composition, as no additional exposure to organic selenium is expected.

2.3.3. Safety for the user

No specific studies were provided regarding the toxicity of the additive on the respiratory system.

Based on the highest concentrations of selenium (44,400 mg Se/kg) and zinc (38,200 mg Zn/kg) in the additive and the highest measured dusting potential of 2344 mg/m^3, the maximum concentrations released in dust during handling could reach 104 mg Se/m^3 and 89.5 mg Zn/m^3, assuming the same proportions of Se and Zn in the dust as in the additive. The respirable fraction was estimated to be 83.3% based on the particle size analysis, therefore the selenium and zinc concentrations in respirable dust would be 87 mg Se/m^3 and 75 mg Zn/m^3, respectively.

These calculated values exceed internationally accepted workplace limits for selenium (0.02 mg/m^3, set by the Deutsche Forschungsgemeinschaft as the maximum concentration in the workplace) (DFG, 2018) and zinc (0.1 mg/m^3) (NIOSH, 2007) and are also above the limits of the time-weighted average (TWA) of zinc chloride (1 mg/m^3) or the TWA of zinc oxide (5 mg/m^3) (NIOSH, 2007). Therefore, the FEEDAP Panel concluded that the additive poses an inhalation risk to users.

Based on dermal and eye irritancy studies that were carried out in accordance with OECD TG 404 and OECD TG 405, respectively, the Zn-L-SeMet-4%Se should be classified as non-irritant to skin and eyes. No data was provided to conclude on the skin sensitisation potential.

The FSA and FSS agree to consider the additive as a potential skin sensitiser, to recommend limiting exposure through inhalation, and to not consider it as an irritant to skin and eyes.

2.3.4. Conclusion on Section III

The FEEDAP Panel concluded that the proposed change to the authorisation terms, involving a higher selenium or zinc concentration in the additive, would not affect consumer or environmental safety. The FEEDAP Panel considered the proposed increase in selenium concentration in the additive to be safe for all animal species. In conclusion regarding user safety, the additive should be classified as non-irritant to skin and eyes, but no conclusion could be drawn on skin sensitization. The additive poses an inhalation risk to users.

The FSA and FSS agree with the view that the additive is safe to the target species, consumers and the environment, despite the proposed changes in composition. The FSA/FSS agree to label the additive as a potential skin sensitiser and that exposure through inhalation should be minimised. The additive is not an irritant to skin and eyes.

2.4. Section IV: Efficacy

The FEEDAP Panel concluded that, since the conditions of use for the additive remain same with those previously authorised, the proposed modifications to the terms of authorisation would not impact the product's efficacy.

The FSA and FSS agree with the view that the additive remains efficacious given no changes in the conditions of use were proposed.

3. Analytical method evaluation

FSA/FSS evaluated the EURL analytical method evaluation, noting it was carried out in 2017, when the UK was still part of the EU and would have participated of their approval. No concerns are raised at this stage for the validity of the methods for UK/GB use, and therefore, the FSA/FSS accept the EURL analytical method evaluation report (EURL, 2017). FSA/FSS determined the analytical method as appropriate for official controls for this feed additive.

4. Conclusions

The FEEDAP Panel concluded Zn-L-SeMet-4%Se with a minimum content of Se of 40 g/kg is safe for all animal species as well as for consumers and the environment, under the authorised conditions of use respecting the maximum supplementation levels of selenium. The additive is non-irritant to skin and eyes, but no conclusion could be drawn on skin sensitization. The additive poses an inhalation risk to users.

The FEEDAP Panel concluded that, since the conditions of use for the additive remain same with those previously authorised, the proposed modifications to the terms of authorisation would not impact the product's efficacy.

5. Recommendation

The FEEDAP Panel noted that the provided data only cover a selenium concentration range of 40–46 g Se/kg. As no information is available for other preparations in the 2–40 g Se/kg range, the Panel recommends adding a new authorisation for preparations with specifications of 40–46 g Se/kg.

6. Caveats and uncertainties

No information was provided for preparation of the additive in the range from 2-40 g Se/kg.

No conclusion can be drawn on the skin sensitisation potential of the additive as no data was provided.

7. FSA/FSS conclusions for GB risk analysis

The application has been assessed in line with the applicable guidance and is partially based on considerations of detailed proprietary information available to the Panel, which were also submitted to the FSA and FSS. The EFSA opinion identifies and characterises the hazards present from the change in content from this proposed modification and there is sufficient information to enable an assessment of exposure, which is also relevant to GB. The risk characterisation is unchanged from the 2018 opinion for most areas, and appropriate evidence was submitted to support the requested modification, including data on safety to the worker. The conclusions of the EFSA opinion have been reviewed in detail by FSA and FSS and are considered appropriate and consistent, including the caveats and uncertainties identified in the opinion which are applicable to GB. Sufficient evidence has been demonstrated to conclude without further questions or risk assessment.

Abbreviations

Abbreviation	Definition
CAS	Chemical Abstracts Service
CV	Coefficient of Variation
EC	European Commission
EU	European Union
EFSA	European Food Safety Authority
EURL	European Union Reference Laboratory
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
FSA	Food Standards Agency
FSS	Food Standards Scotland
GB	Great Britain
OECD	Organisation for Economic Co-operation and Development
RP	Regulated Product
TWA	Time-weighted Average
UK	United Kingdom

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References

EC (European Commission). (2003). *Regulation No 1831/2003 of the European Parliament and of the Council on additives for use in animal nutrition*. https://www.legislation.gov.uk/eur/2003/1831/contents

EC (European Commission). (2008). *Regulation No 429/2008 of the European Parliament and of the Council on additives for use in animal nutrition*. https://www.legislation.gov.uk/eur/2008/429/contents

EC (European Commission). (2019). *Regulation No 2019/49 of the European Parliament and of the Council on additives for use in animal nutrition*. https://www.legislation.gov.uk/eur/2019/49

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2012a). Guidance for the preparation of dossiers for nutritional additives. *EFSA Journal*, *10*(1), 2535. https://doi.org/10.2903/j.efsa.2012.2535

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2012b). Guidance on studies concerning the safety of use of the additive for users/workers. *EFSA Journal*, *10*(1), 2539. https://doi.org/10.2903/j.efsa.2012.2539

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2017a). Guidance on the assessment of the safety of feed additives for the consumer. *EFSA Journal*, *15*(10), 5022. https://doi.org/10.2903/j.efsa.2017.5022

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2017b). Guidance on the assessment of the safety of feed additives for the target species. *EFSA Journal*, *15*(10), 5021. https://doi.org/10.2903/j.efsa.2017.5021

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2017c). Guidance on the identity, characterisation and conditions of use of feed additives. *EFSA Journal*, *15*(10), 5023. https://doi.org/10.2903/j.efsa.2017.5023

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2018a). Guidance on the assessment of the efficacy of feed additives. *EFSA Journal*, *16*(5), 5274. https://doi.org/10.2903/j.efsa.2018.5274

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2018b). Scientific Opinion on safety and efficacy of Zinc-l-Selenomethionine as feed additive for all animal species. *EFSA Journal*, *16*(3), 5197. https://doi.org/10.2903/j.efsa.2018.5197

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2019). Guidance on the assessment of the safety of feed additives for the environment. *EFSA Journal*, *17*(4), 5648. https://doi.org/10.2903/j.efsa.2019.5648

EURL-FA (European Reference Laboratory for Feed Additives). (2017). *CRL Evaluation Report on the Analytical Methods submitted in connection with the Application for Authorisation of Feed Additive according to Regulation (EC) No 1831/2003. Zinc-L-selenomethionine*. https://joint-research-centre.ec.europa.eu/reports-and-technical-documentation/fad-2016-0056_en

NIOSH (National Institute for Occupational Safety and Health). (2007). *Department of health and human services, Centers for Disease Control and Prevention Pocket guide to chemical hazards* (Nos. 2005–149). NIOSH Publications. https://www.cdc.gov/niosh/npg/default.html