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Safety and efficacy of sodium selenate as feed additive for ruminants

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Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of sodium selenate as a nutritional feed additive for ruminants, when used via an intraruminal bolus in ruminants. The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) Panel concludes that based on (i) the estimation of the release of selenium from the bolus, (ii) the similarities in bioavailability with sodium selenite, (iii) the experience with the use of boluses in ruminant nutrition and (iv) the wide margin of safety compared with the maximum tolerable levels of selenium in ruminants, the additive is safe for ruminants. The use of sodium selenate by bolus administration providing a selenium intake not exceeding that resulting from the maximum authorised EU level of total selenium in feed presents no concerns for consumer safety. The additive does not pose a risk to users by inhalation and is considered as non-corrosive but irritant for the skin and the eyes. The FEEDAP Panel considers the additive as a skin sensitiser and respiratory sensitiser. The additive under assessment, in its intended use as complementary feed for ruminants in the form of boluses, is a substitute for other authorised selenium additives and will not further increase the environmental burden of selenium. Based on two studies submitted in cattle and sheep and studies from the literature, the FEEDAP Panel concludes that sodium selenate delivered by a bolus to ruminants is an efficacious source of selenium in meeting the animals' requirements. The Panel posed some recommendations regarding the use of the bolus, especially in small size ruminants. The Panel also posed a remark, concerning the zinc content of the bolus from which the additive is delivered.

Keywords: nutritional additives, compounds of trace elements, selenium, sodium selenate, ruminants, safety, efficacy

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of a feed additive shall submit an application in accordance with Article 7.

The European Commission received a request from Retorte GmbH Selenium Chemicals and Metals[2] for authorisation of the product sodium selenate as feed additive for use in dietetic complementary feeds in the form of a bolus, for ruminants (category: nutritional additives; functional group: compounds of trace elements).

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 4(1) (authorisation of a feed additive or new use of a feed additive). 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 6 December 2017.

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 sodium selenate, when used under the proposed conditions of use (see Section 3.1.6).

1.2. Additional information

Sodium selenate is intended to be used as a source of selenium for ruminants.

The additive 'Sodium selenate' had been authorised in the European Union (EU) under the element Selenium-Se (E8) for all animal species 'Without a time limit' (Council Directive 70/524/EEC concerning additives in feedingstuffs – List of authorised additives in feedingstuffs (2004/C 50/01).[3] Following the provisions of Article 10(1) of Regulation (EC) No 1831/2003, the compound was included in the EU Register of Feed Additives under the category 'Nutritional additives' and the functional group 'Compounds of trace elements'.[4] An application dossier for re-evaluation as a feed additive according Article 10(2) of Regulation (EC) No 1831/2003 was submitted to the European Commission, but subsequently withdrawn. The authorisation of sodium selenate was then withdrawn by Commission Implementing Regulation (EU) 2017/1145 of 8 June 2017.[5]

Sodium selenate has been assessed by the Committee for Medicinal Products for Veterinary Use of the European Medicine Agency (EMA) who recommended the maintenance of the existing maximum residue level (MRL) classifications for this compound in all food producing species (EMA, 2015).

The National Toxicology Program (NTP) of the USA assessed some toxicological studies on sodium selenate (NTP, 1994). Sodium selenate is authorised for use in feed in the USA.[6]

In the context of the Codex Alimentarius, the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) drew in 1979 advisory lists of nutrient compounds for use in foods for special dietary uses intended for infants and young children, in which sodium selenate is included (Codex Alimentarius, 2008).

Sodium selenate is authorised for use in food as a mineral substance which may be used in the manufacture of food supplements (Regulation (EC) No 1170/2009)[7] and which may be added to foods

[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] Retorte GmbH Selenium Chemicals and Metals Sulzbacher Str. 45 D-90552 Röthenbach a.d. Pegnitz.
[3] OJ C 50, 25.2.2004, p. 1.
[4] European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. http://ec.europa.eu/food/food/animalnutrition/feedadditives/docs/comm_register_feed_additives_1831-03.pdf
[5] Commission Implementing Regulation (EU) 2017/1145 of 8 June 2017 on the withdrawal from the market of certain feed additives authorised pursuant to Council Directives 70/524/EEC and 82/471/EEC and repealing the obsolete provisions authorising those feed additives. OJ L 166, 29.6.2017, p. 1.
[6] CFR - Code of Federal Regulations Title 21. Available online: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=573.920
[7] Commission Regulation (EC) No 1170/2009 of 30 November 2009 amending Directive 2002/46/EC of the European Parliament and of Council and Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards the lists of vitamin and minerals and their forms that can be added to foods, including food supplements. OJ L 314, 1.12.2009, p. 36.

(Regulation (EC) No 1925/2006)[8]; sodium selenate is also authorised as a substance that may be added for specific nutritional purposes in foods for particular nutritional uses (Commission Regulation (EC) No 953/2009).[9] Regarding pharmacologically active substances and their classification regarding MRLs in foodstuffs of animal origin, sodium selenate listed in Table 1 of the Annex of Regulation 37/2010[10] as 'Allowed substances, no MRL required'. According to the Annex to Regulation (EC) No 432/2012[11] the following health claims can be made only for food which is at least a source of selenium as referred to in the claim SOURCE OF [NAME OF VITAMIN/S] AND/OR [NAME OF MINERAL/S] as listed in the Annex to Regulation (EC) No 1924/2006: 'Selenium contributes to normal spermatogenesis', 'Selenium contributes to the maintenance of normal hair', 'Selenium contributes to the maintenance of normal nails', 'Selenium contributes to the normal function of the immune system', 'Selenium contributes to the normal thyroid function', 'Selenium contributes to the protection of cells from oxidative stress'.

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[12] in support of the authorisation request for the use of sodium selenate as a feed additive for ruminants in the form of a bolus.

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 expert's elicitation knowledge, to deliver the present output.

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in a previous assessment are valid and applicable for the current application.[13]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of sodium selenate is in line with the principles laid down in Regulation (EC) No 429/2008[14] and the relevant guidance documents: Guidance on nutritional additives (EFSA FEEDAP Panel, 2012a), Technical guidance on Tolerance and efficacy studies in target animals (EFSA FEEDAP Panel, 2011a), Technical Guidance for assessing the safety of feed additives for the environment (EFSA, 2008), Guidance for the preparation of dossiers for additives already authorised for use in food (EFSA FEEDAP Panel, 2012b), Guidance for establishing the safety of additives for the consumer (EFSA FEEDAP Panel, 2012c) and Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012d).

3. Assessment

The additive under assessment is sodium selenate for use as a nutritional additive, functional group compounds of trace elements in complementary feed for ruminants, in the form of boluses. This inorganic compound was authorised in the EU as a nutritional feed additive for all animal species and used in animal nutrition as a source of the essential trace element selenium for decades. The safety and efficacy assessment of the additive is based on its use in boluses, with the specific composition reported in the technical dossier[15] (Table 1).

[8] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods . OJ L 404, 31.12.2006, p. 26.
[9] Commission Regulation (EC) No 953/2009 of 13 October 2009 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses. OJ L 269, 14.10.2009, p. 9.
[10] 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.
[11] Commission Regulation (EC) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health. OJ L 136, 25.5.2012, p. 1.
[12] FEED dossier reference: FAD-2017-0045.
[13] The report linked to the previous dossier (related to EFSA-Q-2014-00506) is available on the EURL website: https://ec.europa.eu/jrc/en/eurl/feed-additives/evaluation-reports/fad-2010-0149
[14] 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.
[15] Technical Dossier/Supplementary Information/Annex II-II-20.

Besides sodium selenate at a concentration of 0.332%, the boluses contain other authorised feed additives (calcium iodate and cobalt carbonate) and a number of excipients (composition provided by the applicant, Table 1).

Table 1: Composition of the boluses

	CAS No.	Concentration % (w/w)	
		Cattle	Sheep
Feed Additives			
Calcium iodate	7789-80-2	4.074	2.50
Sodium selenate	13440-01-0	0.332	0.332
Cobalt carbonate	51839-24-8	0.583	0.583
Excipients			
Zinc Ballast	7440-66-6	82.960	84.560
Soft Paraffin Wax	8002-74-2	3.564	4.750
Hard Paraffin Wax	8002-74-2	6.653	6.416
Microcrystalline Wax	63231-60-7	1.664	0.713
Sunflower Oil	8001-21-6	0.120	0.115
Sipernat	112926-00-8	0.050	0.025
BHT	128-37-0	–	0.005

CAS: Chemical Abstracts Service.

The selenium content of grain and forages is generally low in most European countries; therefore, livestock is routinely supplied with extra dietary selenium in order to avoid selenium deficiency (Abd El Ghany and Tórtora-Pérez, 2010).

3.1. Characterisation

The active compound under assessment is sodium selenate. The active compound coincides with the additive under assessment. The FEEDAP Panel notes that the characterisation described in the paragraphs below (Sections 3.1.1 to 3.1.6) refers only to the additive 'sodium selenate', not to the complementary feed (bolus) in which the additive will be incorporated.

3.1.1. Characterisation of the additive

Sodium selenate (International Union of Pure and Applied Chemistry (IUPAC) name disodium selenate) is identified by Chemical Abstracts Service (CAS) number 13410-01-0 and the European Inventory of Existing Commercial chemical Substances (EINECS) number 236-501-8. Sodium selenate has the chemical formula Na_2SeO_4 (molecular weight 188.94 Da, theoretical selenium content 41.8%).

The additive contains by specification ≥ 41% selenium. The applicant provided analytical data of five batches of the additive showing a selenium content within a range of 41.6 to 41.8%.[16] The applicant stated that the active component is Selenium (VI); however, no evidence was submitted about the selenium speciation (the selenium content of sodium selenate was analysed by gravimetry).[17]

The same five batches were analysed for impurities, including lead (Pb), arsenic (As), cadmium (Cd), mercury (Hg), nickel (Ni), copper (Cu), iron (Fe) and tellurium (Te).[18] The results reported were (in mg/kg additive): Pb < 0.5–2, As < 0.5, Cd < 0.03, Hg < 0.1–0.1, Ni < 0.2–0.4, Cu < 0.1–0.7, Fe 0.6–3.9 and Te < 0.1–2.5.[19] The applicant submitted eight further analyses on nickel content in the additive, showing values from < 0.2 to 1.5 mg/kg.[20] Dioxins and the sum of dioxin plus dioxin-like PCBs was measured in six batches, showing average contents of 0.5 ng WHO-PCDD/F-TEQ/kg and 0.12 ng WHO-PCDD/F-PCB-TEQ/kg additive, respectively.[21] The concentrations of the undesirable

[16] Technical Dossier/Section II/Annex II- II-5; Technical Dossier/Supplementary Information/Annexes II-II-1 to II-II-5.
[17] Technical Dossier/Section II/Annex II- II-17.
[18] Technical Dossier/Section II/Annex II- II-5.
[19] Values preceded by the sign '<' mean the Limit of Quantification (LOQ). Technical Dossier/Supplementary Information.
[20] Technical Dossier/Supplementary Information.
[21] Technical Dossier/Supplementary Information/Annexes II-II-6 to II-II-8.

substances analysed comply with those set in Directive 2002/32/EC[22] for compounds of trace elements; the concentrations of mercury in the additive, for which no specific entry for trace elements is described in the said Directive, do not represent a concern. The elements nickel and tellurium are not listed in the undesirable substances Directive; a safety assessment has been done in the context of their content in the additive.

3.1.2. Physical state of the additive

The additive is a white odourless powder. It is highly soluble in water (840 g/L at 35°C).

Particle size distribution was examined by the sieving technique in the same five batches analysed for the composition[23]; particles (w/w) below 1,000 μm averaged 99.2%, < 300 μm 54.2%, < 150 μm 8.1% and < 75 μm 2.3%. Three recent batches were additionally analysed with a 45 μm sieve; the results showed that the additive contains 1.8–3.2% of particles < 45 μm.[24]

The applicant provided analytical data on dusting potential (by the Stauber–Heubach method) from three bathes of the additive, showing values from 0.1 to 0.3 g/m^3.[25] Data from other two batches of the additive were analysed for selenium in the dust; the results showed high variability[26]: 29,331 and 1,466 μg Se/50 g dust; no further data on selenium analysis in the dust were provided.[20]

3.1.3. Manufacturing process

[redacted]

3.1.4. Stability and homogeneity

For compounds of trace elements stability studies are generally not required and were not provided. The applicant indicated that when using the material after three years from manufacturing, a retest prior to use is recommended, comprising visual inspection and moisture determination.

In order to demonstrate homogeneous distribution of the additive in the boluses formulation, three tests were carried out, each in a bolus intended for a specific animal: lamb,[27] sheep[28] and adult cattle.[29] A batch of premix was mixed on site using a Winkworth RT80 mixer. Six samples were taken from a variety of points in the mix and selenium was analysed. The target concentration of selenium in these products was of 1,378 mg/kg. The relative standard deviation related to the selenium content was of 3% for each premix of lamb, sheep and cattle.

3.1.5. Physico-chemical incompatibilities or interactions

Very strong reducing agents are able to transform the selenate into selenite or elemental selenium. Such strong reducing agents are indeed present in the bolus: elemental zinc[30]; since it is in large excess, it is very likely that all the selenate is converted to selenite, perhaps already in the boluses and almost certainly in the rumen.

3.1.6. Conditions of use

The additive is intended to use as a nutritional additive in all ruminants species and categories.

[22] Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed. OJ L 140, 30.5.2002, p. 10.
[23] Technical Dossier/Section II/Annexes II- II-5; Technical Dossier/Supplementary Information/Annexes II-II-9 to II-II-13.
[24] Technical Dossier/Supplementary Information/Annexes II-II-14 to II-II-16.
[25] Technical Dossier/Supplementary Information/Annexes II-II-17 to II-II-19.
[26] Technical Dossier/Section II/Annexes II-II-6 and II- II-7.
[27] Technical Dossier/Section II/Annexes II-II-12.
[28] Technical Dossier/Section II/Annexes II-II-13.
[29] Technical Dossier/Section II/Annexes II-II-14.
[30] Standard redox potentials are E° = 0.76 V for Zn (s) ↔ $Zn^{2+}+2e^-$, E° = 0.82 V for $SeO_4^{2-}+2H^+ +2e^-$ ↔ $SeO_3^{2-}+H_2O$, i.e. reduction in alkaline conditions, and E° = 1.15 V for $HSeO_4^- +3H^+ +2e^-$ ↔ $H_2SeO_3^{2-}+ H_2O$, i.e. reduction in acidic and neutral conditions.

The maximum content of total selenium authorised in feed is set to 0.5 mg/kg complete feed. The proposed method of administration of sodium selenate is in the form of boluses, throughout a dietetic complementary feed used as an orally administered intraruminal device.

The selenium release rates from the bolus must be limited to respect the levels calculated from the legally binding maximum concentration of selenium in complete feed and the feed intake of the animal.

The applicant provided details on the use of the sodium selenate in the boluses to perform the release rate calculation and the release assessment on cattle and sheep.[31] In particular, details on the bolus size to be used in adult cattle, growing cattle and adult sheep, corresponding to 160 g, 130 g and 48 g, respectively, were provided; the mean daily release of selenium from the boluses over 180 days was reported as 1.2, 1.0 and 0.4 mg, respectively.

The mean daily release is a value derived from the physical erosion rate of the bolus in the rumen and biochemical responses following bolus administration. The applicant only provided information from a study performed with cows with the bolus intended for adult cattle (bolus of 160 g); see section 3.2.1. The overall mean weekly weight loss of the bolus was 7.12 g (95% CI 4.68–9.56 g). The calculation of selenium release from the bolus shows for upper 95% confidence interval of weight loss 1.92 mg Se/day. The maximum allowable level of selenium is 0.5 mg/kg of complete feed at 88% dry matter (DM). Default value for daily feed intake is 20 g DM/kg body weight for cattle for fattening (EFSA FEEDAP Panel, 2017); thus, for 400-kg animal, the maximum allowable level of selenium in the diet is 4.5 mg Se/day. Based on the upper 95% confidence interval of the overall mean weekly losses, the bolus provides 43% of the maximum allowable level of selenium in the diet.

3.2. Safety

The feed additive under assessment is sodium selenate. For the evaluation of the safety of the additive, the FEEDAP Panel assessed the safety of selenium under the conditions of use of the additive; the Panel wishes to highlight that the safety of the bolus regarding its composition is not the subject of this scientific opinion. Additionally, the Panel considered for the safety assessment the nickel and tellurium contained in the additive.

3.2.1. Selenium release from sodium selenate in boluses

In order to assess the safety of sodium selenate from its use via bolus, the FEEDAP Panel performed some calculations to estimate the release of selenium from the bolus. These calculations were based on default values for feed intake indicated in the Guidance on the safety for target species (EFSA FEEDAP Panel, 2017) and the release of selenium from the bolus, without the contribution of selenium from the basal diet.

The FEEDAP Panel notes that the data on the bolus release of selenium (mg/day) were provided by the applicant for 180 days; however, the measurements of the bolus size provided in the experiment performed with the fistulated adult cattle reached 126 days only. These data were obtained from an *in vivo* study with three fistulated cows. The weight of the bolus at the start of the experiment was approximately 160 g. At weekly intervals, the boluses were removed from each cow and weighed; after weighing, the boluses were returned to the rumen via the ad hoc cannula. Boluses were present in all three cows when the trial was stopped after 126 days, since the small size of the bolus precluded finding it in the rumen.[31] By the other hand, the applicant reported uncertainties regarding the release of selenium in the bolus of sheep and gave the range of 0.4–0.6 mg/day, the former corresponding to a release during 180 days and the latter for a release during 120 days (see Section 3.3.2). Owing to these considerations, the FEEDAP Panel opted to calculate the release of selenium from bolus in the relevant species/categories using the scenarios of 180 and 120 days (Table 2).

[31] Technical Dossier/Supplementary Information/Annex II-II-21.

Table 2: Calculations of the selenium (Se) release from the bolus in different ruminant species/categories and comparison with maximum authorised levels of selenium in complete feed for these target animals

Species/ categories	Feed intake (kg DM)(1)	Feed intake (kg 88% DM)	Max. Se intake (mg/day)(2)	Bolus release Se (mg Se/day) 180/120 days(3)	Bolus release Se (% max Se authorised)(4) 180/120 days
Dairy cow (650 kg)	20	22.7	11.4	1.2/1.8	10.5/15.8
Cattle for fattening (400 kg)	8	9.1	4.5	1.0/1.5	22.2/33.3
Adult sheep (60 kg)	1.2	1.4	0.7	0.4/0.6	58.8/88.2

DM: dry matter.
(1): Default values for feed intake indicated in the Guidance on the safety for target species (EFSA FEEDAP Panel, 2017).
(2): Maximum selenium intake considering authorised total selenium in feed 0.5 mg Se/kg.
(3): Daily release of selenium from bolus (selenium content in different type of boluses divided by 180 or 120).
(4): The comparison of daily selenium release from bolus with maximum allowable level of selenium intake (100%).

Data on release of selenium from the bolus were not provided. The FEEDAP Panel notes that a higher release may occur during the first period of bolus life (see also Table 4). However, for the cattle and dairy cows, considering that the maximum calculated release compared to the authorised levels in feed was up to 33%, it would be unlikely to reach the maximum authorised comparable selenium content in complete feed.

Due to the high release of selenium in sheep (up to 88% of the maximum authorised selenium in sheep feed), the FEEDAP Panel performed also the analogue calculations for growing lambs and for small breed of sheep. These calculations were based on the feed intake values reported by the National Research Council (NRC, 1987) and the release of selenium from the bolus (data provided by the applicant) – without the contribution of selenium from the basal diet – and considered the same two scenarios as in the case of adult sheep (Table 3).

Table 3: Calculations of the selenium release from the bolus in growing lambs and small breed of sheep and comparison with maximum authorised levels of selenium (Se) in complete feed for these target animals

Category of animals	Feed intake (kg DM)(1)	Feed intake (kg 88% DM)	Max. Se intake (mg/day)(2)	Bolus release Se (mg Se/day) 180/120 days(3)	Bolus release Se (% max Se authorised)(4) 180/120 days
Growing lambs Live weight (kg)/daily weight gain (g)					
20/100	0.63	0.72	0.36	0.4/0.6	111/167
20/300	1.09	1.24	0.62	0.4/0.6	65/97
30/200	1.10	1.25	0.63	0.4/0.6	64/96
30/400	1.55	1.76	0.88	0.4/0.6	46/68
40/250	1.44	1.64	0.82	0.4/0.6	49/73
40/500	1.96	2.23	1.12	0.4/0.6	36/54
Adult sheep (40 kg)					
Maintenance	0.77	0.88	0.44	0.4/0.6	91/137
Breeding	0.85	0.97	0.48	0.4/0.6	83/124
Gestation (single lamb)	0.99	1.13	0.56	0.4/0.6	71/107
Lactation (single lamb)	1.09	1.24	0.62	0.4/0.6	65/97

DM: dry matter.
(1): Feed intake values reported by the National Research Council (NRC, 1987).
(2): Maximum selenium intake considering authorised total selenium in feed 0.5 mg Se/kg.
(3): Daily release of selenium from bolus (selenium content in bolus divided by 180 or 120).
(4): The comparison of daily selenium release from bolus with maximum allowable level of selenium intake (100%).

Based on these calculations, the intake of selenium from the sodium selenate bolus would in some cases exceed the authorised level in complete feed; this could be the case in small growing lambs with 20 kg or less body weight and in small breeds of sheep (body weight 40 kg and less).

The FEEDAP Panel notes that an uncertainty related to the selenium content in the basal diets may have led to an underestimation of the total selenium intake by the animals, and therefore on the possibility to exceed the maximum authorised content of total selenium in complete feed, especially for ovine.

3.2.2. Safety for the target species

No tolerance study conducted with the additive under assessment was provided to support the safety of the additive for the target species. The applicant argued that these studies can be omitted based on the facts that sodium selenate (i) had been previously authorised as a feed additive under Directive 70/524/EEC; (ii) is chemically similar and with comparable bioavailability to sodium selenite (107 ± 11.5%; Jongbloed et al., 2002) currently authorised in the EU and (iii) there is a broad historical knowledge on selenium supplementation in animal nutrition. The FEEDAP Panel notes that it is likely that the selenate is converted to selenite due to the presence of metallic zinc in the bolus.

The applicant performed a structured literature search on the use of selenium boluses in ruminants.[32] The databases consulted were PubMed and Agris and the search period covered from 1980 to 2018 for the former database and unlimited for the latter; the keywords used were: 'selenium', 'selenate', 'ruminant bolus', 'bolus'. A total of 185 references were retrieved; from those, the applicant considered relevant 21 references.

The FEEDAP Panel reviewed those references; most of them were considered not suitable for this assessment since: (i) were performed in non-ruminant species; (ii) the source of selenium was not sodium selenate; (iii) sodium selenate was not administered as a bolus; or (iv) no information was available on the source of selenium in the bolus. Only four papers could be considered partially relevant for this assessment (use of sodium selenate as a bolus in ruminant species): one was conducted in cattle (Sprinkle et al., 2006) and three in goat (Serra et al., 1996; Fujihara et al., 2006; Hayashida et al., 2006 – all from the same research group); however, none of them was a proper tolerance study, since the animals received an adequate dose of sodium selenate (together with other trace elements as cobalt and iodine).[33] All these studies were considered 'field trials' performed in ruminants fed on local pastures with the objective to provide a long-term mineral supplementation to cover the physiological needs and improve productivity. In all these studies, the bolus demonstrated to be effective to improve the selenium status of the animals, maintaining selenium serum concentrations within the adequate range. None of these papers contained experimental data about the release of selenium from the boluses; only data from the bolus supplier were available: 3.4 mg Se/day in the cattle study (in the current application proposed selenium releases are 1.2 and 1.0 mg Se/day in cattle and growing cattle respectively) and 0.13 mg Se/day in the goat references (no conditions of use have been specified for this ruminant species in the current application). No adverse effects of the use of the boluses containing sodium selenate were observed in any of these experiments.

The FEEDAP Panel has calculated the release of selenium from the bolus in the different ruminants species/categories (see Section 3.2.1). According to these calculations, the release of selenium may exceed the maximum authorised in complete feed (0.5 mg Se/kg) in growing lambs or small ovine breeds. However, the FEEDAP Panel notes that the maximum selenium level authorised in complete feed is about one order of magnitude below the maximum tolerable levels (MTLs) in feed for ruminants (5 mg Se/kg feed dry matter (DM) for cattle and sheep; NRC, 2005).

Nickel and tellurium were reported as contaminants in the additive in concentrations up 1.5 and 2.5 mg/kg of the additive, respectively. The calculation of the contribution of nickel and tellurium to the bolus of adult cattle (160 g), is about 0.80 μg Ni and 1.3 μg Te, respectively, corresponding to about 5 μg Ni and 8 μg Te per kg bolus. The background nickel in feed has been reported as 4 mg/kg DM feed (Nicholson et al., 1999; Van Paemel et al., 2010). The background tellurium in feed materials has been reported in the range of 13 to 350 μg per kilogram (Kabata-Pendias, 2010). Therefore, the contribution of nickel or tellurium to the ruminant diet from the additive would be negligible and, thus, no concerns for the safety for target animals are expected.

[32] Technical Dossier/Supplementary Information/Section III.
[33] COSECURE™ Bolus. https://www.cosecureboluses.com/

3.2.2.1. Conclusions on safety for the target species

Based on (i) the estimation of the release of selenium from the bolus in ruminants, (ii) the similarities in bioavailability with sodium selenite, (iii) the experience with the use of boluses in ruminant nutrition and (iv) the wide margin of safety compared with the maximum tolerable levels of selenium in ruminants, the FEEDAP Panel concludes that sodium selenate administered by a complementary feed in the form of a bolus is safe for ruminants.

3.2.3. Safety for the consumer

Sodium selenate is an inorganic compound of selenium, providing a selenium bioavailability comparable to the standard inorganic source sodium selenite; limited data summarised by Jongbloed et al. (2002) suggest that, taking sodium selenite as a benchmark (= 100), the mean relative biological value of sodium selenate is 107 (three studies ranging from 98 to 107 and one 124). Sodium selenite is safe for consumers when used as a feed additive up to the maximum level of total selenium in feed authorised in the EU (EFSA FEEDAP Panel 2015, 2016a,b). The FEEDAP Panel considers that, for inorganic selenium sources, indicators of bioavailability can provide information also on deposition.

Only one study on selenium deposition in edible tissues and products, upon bolus administration was provided; this trial assessed selenium levels in the blood, liver, kidney and muscle of sheep for fattening (6-month old) after the administration of iron/selenium pellets or soluble-glass boluses (Millar and Meads, 1988).[34] This study was performed with two groups of six sheep and lasted four months; however, three out of six animals given a soluble-glass bolus lost the boluses over the 4 months of the trial. Another group of six sheep was left untreated. The composition of pellets was 5% elemental selenium and 95% iron by weight; mean mass and density was 10.2 g and 5.9 g/mL, respectively. The composition of soluble-glass bolus was 0.25% selenium, 0.50% cobalt and 13.2% copper by weight, with mean mass and density of 36.0 g and 2.8 g/mL, respectively.[35] Background content of feed (pasture) was 0.02 mg Se/kg DM. The release rate from pellets or bolus was not calculated. At the end of the trial, sheep fed the pellets had a higher selenium concentration in liver (average 6.34 μmol/kg wet weight vs. 3.54 for bolus and 0.71 in controls); in both treated groups the selenium concentration in kidney was around 12.0 μmol/kg wet weight, vs. 5.25 in controls. A numerical increase of selenium concentration in muscle was elicited by pellet treatments (0.75 μmol/kg wet weight) vs. bolus (0.50) and controls (0.25).

Whereas the FEEDAP Panel notes that the many limitations of the study above described (the very small number of bolus-treated animals, no measurement of selenium release) prevent reaching any firm conclusions, there are no indications that bolus administration will cause a different or higher deposition, compared to a control group, in edible tissues. No data are available for ruminant milk, but it is unlikely that selenium excretion in milk would be essentially influenced by bolus administration *per se*.

The results of the efficacy study in cattle for fattening in which selenium in liver was measured might be also relevant to support deposition of selenium from sodium selenate. Deposition of selenium in liver during the study was higher in the bolus-treated group than in the positive or negative controls (see Section 3.3.1).

No safety concerns for consumers are foreseen when inorganic selenium compounds are supplemented to feedingstuffs up to the maximum levels of total selenium authorised in the EU (0.5 mg Se/kg). On the other hand, feed supplementation above the maximum authorised levels may lead to selenium intake above the UL (EC, 2000); this would pose a concern to consumer safety (see EFSA FEEDAP Panel, 2011b, 2012a–d). The FEEDAP Panel retains that the same considerations apply to selenium administration by bolus.

3.2.3.1. Conclusions on safety for the consumer

The use of sodium selenate by bolus administration providing a selenium intake not exceeding that resulting from the maximum authorised EU level of total selenium in complete feed presents no concerns for consumer safety.

3.2.4. Safety for the user

A systematic database search, using four public databases (PubMed, PubMed Central, Medline and Agris), was performed by the applicant for the period 1890–2010, using the keywords 'selenium' and

[34] Technical Dossier/Supplementary information/Section III/Annex II-III-32SIn.
[35] From COSECURE™.

'intoxication'; the databases consulted gave a large number of hits, but only 0.4% to 19.2% of them turned out to be relevant in humans or domestic animals: 15 accidental, 3 suicidal, 3 criminal and 3 occupational intoxication cases were retrieved.[36] An additional data search for the time frame 2010 to 2018 was performed on PubMed giving 48 hits, 10 of them were considered relevant; six of these relevant hits were related to humans but they referred to accidental events or had natural root causes.[37]

No accidental or occupational intoxication having its origin in feed production or farming activities was retrieved from the searches described above.

3.2.4.1. Effects on the respiratory system

The most likely exposure route to sodium selenate at the workplace is by inhalation. The applicant refers to a study performed with rats (Wistar, male/female) in 2012 according EU Method B.2 (Acute Toxicity by Inhalation) established a LC_{50} (4 h) between 0.052 and 0.51 mg/L air, but no access to the report was provided.[32]

The highest dusting potential of the additive was 0.3 g/m^3 and the selenium concentration in the dust was 586.6 mg Se/kg (maximum analysed value: 29331 μg Se/50 g dust – see Section 3.1.2). It can therefore be calculated that a maximum concentration of 176 μg Se/m^3 could be released by the dust when handling the additive. Considering that 3.2% of the particles were < 45 μm (see Section 3.1.2) an estimation of selenium from dust that could reach the thoracic level would be about 5.6 μg/m^3.

The maximum tolerable air concentrations for selenium compounds have been set by different organisations (e.g. German Maximale Arbeitsplatz Konzentration (MAK) List, Occupational Safety and Health Administration (OSHA), National European Authorities) between 0.02 and 0.2 mg Se/m^3. Thus, the selenium content in the dust do not pose concerns to users by inhalation.

The tellurium content in the additive is up to 2.5 mg/kg. Following the same approach that was described above for selenium, an estimation of 0.24 μg Te/m^3 could reach the thoracic level. Considering that the permissible exposure limit (OSHA, 2018), the threshold limit (ACGIH, 2012) and the German MAK (DFG, 2015) values in the dust or fume are of the same level of 0.1 mg Te/m^3, the tellurium content in the dust does not pose concerns to users by inhalation.

The nickel maximum content of the additive is up to 1.5 mg/kg. The dusting potential of the additive mounted up to 0.3 g/m^3, corresponding to about 0.45 μg Ni/m^3. Considering that the proposed occupational exposure limit (OEL) for the inhalable fraction of water-soluble nickel is 10 μg Ni/m^3 (EC, 2011), a risk related to nickel inhalation is not expected. However, due to the presence of nickel in the additive, it should be considered as a respiratory sensitiser.

3.2.4.2. Effects on the eyes and skin

Two studies performed with the human skin model EpiDerm showed that sodium selenate is considered as irritant but non-corrosive; sensitising effects were not observed. No further information on the above two studies was provided.[32] Nevertheless, owing to the presence of nickel (up to 1.5 mg/kg) and given the well-known sensitisation potential of the metal (EC, 2011) the additive should be considered as a skin sensitiser.

The applicant also reported that sodium selenate showed no effects on the cornea of the bovine eye; the calculated IVIS (*in vitro* irritancy score) was 0.133. Therefore, sodium selenate is classified as 'non-corrosive' and/or 'no severe irritant' according to OECD Guideline no. 437 (2009).[38] However, no access to the relevant report was provided. Considering the skin irritation potential and the possible respiratory irritation, a classification of the additive as slightly irritant for the eyes was considered appropriate.[32]

3.2.4.3. Conclusions on safety for the user

The additive does not pose a risk to users by inhalation.

The additive is considered as non-corrosive but irritant for the skin and for the eyes.

The FEEDAP Panel considers the additive as a skin sensitiser and as a respiratory sensitiser.

[36] Technical Dossier/Supplementary Information/Section III/Annexes II-III-4 to II-III-87.

[37] Technical Dossier/Supplementary Information/Section III/ Annexes II-III-1SIn to II-III-10SIn.

[38] According to OECD Guideline no. 437 (2009), a substance that induces and IVIS > 55.1 is defined as a corrosive or severe irritant.

3.2.5. Safety for the environment

In previous opinions, the FEEDAP Panel assessed the safety for the environment of the inorganic source of sodium selenite when used in animal nutrition up to the maximum authorised content in feed and concluded that not concerns to the environment were expected (EFSA FEEDAP Panel, 2015, 2016a,b). The additive under assessment, sodium selenate for use in complementary feed for ruminants in the form of ruminal boluses, is intended to be a substitute for other authorised selenium additives and will not further increase the environmental burden of selenium.

3.3. Efficacy

3.3.1. Efficacy for cattle

A field study [redacted] was carried out to investigate the effect on liver and blood selenium levels of an intraruminal mineral bolus containing selenium as sodium selenate [redacted]

[redacted]

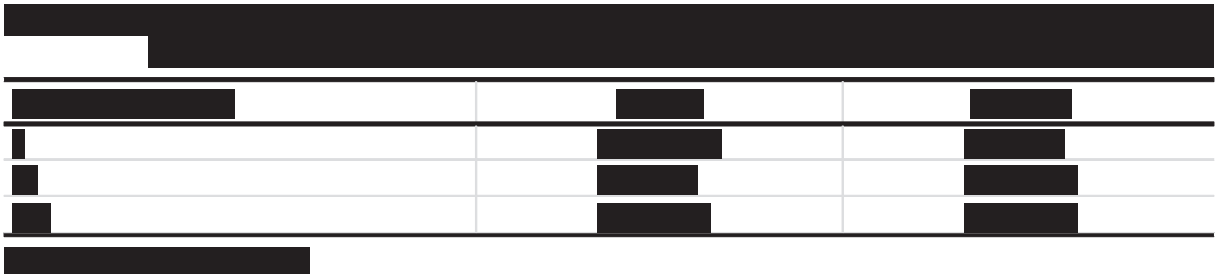
[redacted]. In

[redacted]

conclusion, the bolus with sodium selenate was an effective way of maintaining normal levels of selenium in cattle for at least 168 days.

3.3.2. Efficacy for sheep

A study to evaluate the effect of selenium status on rates of fertility and prolificacy of a selenium supplement in the form of a bolus on selenium deficient in ewes was provided [redacted]



[redacted] The authors concluded that the bolus with sodium selenate was an effective way of restoring and maintaining normal activity of GSHPx in breeding sheep for at least 118 days.

Although the study presents some weaknesses, i.e. the reporting of the statistical analysis and raw data, it shows the effectiveness of selenium supplementation by bolus.

3.3.3. Studies from literature

The studies reviewed by the FEEDAP Panel in the section of safety for target species (see Section 3.2.2) demonstrate that sodium selenate delivered by a bolus is effective to improve the selenium status of the animals, maintaining selenium serum concentrations within the adequate range during the selenium release period.

3.3.4. Conclusions on efficacy

Based on two studies submitted in cattle and sheep and studies from the literature, the FEEDAP Panel concludes that sodium selenate delivered by a complementary feed in the form of a bolus to ruminants is an efficacious source of selenium in meeting the animals' requirements.

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[41] and Good Manufacturing Practice.

[redacted]

[41] 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.

4. Conclusions

Based on (i) the estimation of the selenium release from the bolus in ruminants, (ii) the similarities in bioavailability with sodium selenite, (iii) the experience with the use of boluses in ruminant nutrition and (iv) the wide margin of safety compared with the maximum tolerable levels of selenium in ruminants, the FEEDAP Panel concludes that sodium selenate administered by a complementary feed in the form of a bolus is safe for ruminants.

The use of sodium selenate by bolus administration providing a selenium intake not exceeding that resulting from the maximum authorised EU level of total selenium in feed presents no concerns for consumer safety.

The additive does not pose a risk to users by inhalation. The additive is considered as non-corrosive but irritant for the skin and the eyes. The FEEDAP Panel considers the additive as a skin sensitiser and as a respiratory sensitiser.

The additive under assessment, in its intended use as complementary feed for ruminants in the form of boluses, is a substitute for other authorised selenium additives and will not further increase the environmental burden of selenium.

Based on two studies submitted in cattle and sheep and studies from the literature, the FEEDAP Panel concludes that sodium selenate delivered by a complementary feed in the form of a bolus to ruminants is an efficacious source of selenium in meeting the animals' requirements.

5. Recommendations

The FEEDAP Panel recommends to adapt the size/weight/number of the bolus to both the weight of the animals and the selenium content of the basal diet in order not to exceed the maximum authorised level of selenium in complete feed. The Panel notes that this is especially critical in small-sized ruminants, including growing lambs and kids, veal cattle and small-sized breeds of sheep or goats. Consequently, and with special attention to small-sized ruminants, the supplementation of sodium selenate via bolus should be restricted to animals reared on pasture in selenium-deficient areas.

The label of the additive should specify (i) the use of the additive under the proposed conditions of use, (ii) to be used in ruminants reared on pastures, and (iii) the release life time of the additive administered by boluses (i.e. 180 days for cattle and 118 days for sheep, for the application under assessment).

6. Remarks

The FEEDAP Panel wishes to note that the safety and efficacy assessment of sodium selenate has been performed only for the use of the additive in the form of a bolus; furthermore, the evaluation has been done with the specific boluses described in the dossier.

The FEEDAP Panel identified that the bolus proposed by the applicant contains a high amount of zinc as excipient (up to 85%). Even if the form is poorly bioavailable (elemental zinc), the FEEDAP Panel considers that this material should be used within the maximum authorised levels of zinc in ruminant complete feed in the EU, corresponding to 120 mg Zn/kg complete feed. A detailed appraisal of the zinc intake through the bolus excipient and its impact on safety for the animals, the consumers, the users and the environment is provided in Appendix A.

In summary, the FEEDAP Panel highlights that:

(i) the animals receiving the boluses may meet their zinc needs already through the forage,
(ii) in the case of sheep, the zinc contained in the bolus could lead to an exceedance of the maximum authorised zinc in feed. Accordingly, the FEEDAP Panel stresses its general recommendation for a tailored design of the bolus to the weight of the animals,
(iii) no concerns for consumers or the environment are identified if the maximum level of zinc delivered by the bolus is compatible with the total zinc content authorised in complete feed, and
(iv) the zinc content of the bolus represents a risk to users by inhalation.

Finally, it should be considered that the above remarks do apply to a zinc ballast product with no nanoparticles the FEEDAP Panel strongly stresses the need of specifications in particle size distribution for the zinc elemental ballast used as excipient in the bolus manufacture.

Documentation provided to EFSA/Chronology

Date	Event
7/8/2017	Dossier received by EFSA. Sodium selenate. Submitted by Retorte GmbH Selenium Chemicals and Metals
31/8/2017	Reception mandate from the European Commission
6/12/2017	Application validated by EFSA – Start of the scientific assessment
7/3/2018	Comments received from Member States
8/5/2018	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 for target species, safety for the consumer, safety for the user and efficacy*
14/5/2018	Clarification teleconference during risk assessment with the applicant according to the "EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products"
21/1/2019	Reception of supplementary information from the applicant – Scientific assessment re-started
3/7/2019	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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Abbreviations

bw	body weight
CAS	Chemical Abstracts Service
DM	dry matter
EINECS	European Inventory of Existing Commercial chemical Substances
EMA	European Medicine Agency
EURL	European Union Reference Laboratory
FAO	Food and Agriculture Organization of the United Nations

FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
FM	fresh matter
IUPAC	International Union of Pure and Applied Chemistry
IVIS	*in vitro* irritancy score
MAK	German Maximale Arbeitsplatz Konzentration
MRL	maximum residue level
MTL	maximum tolerable level
NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzo(*p*)dioxins
PCDF	polychlorinated dibenzofurans
TEQ	toxic equivalent
WHO	World Health Organization

Appendix A – Safety assessment of elemental zinc as excipient of sodium selenate bolus

The FEEDAP Panel identified that the bolus proposed by the applicant contains a high amount of zinc as excipient (up to 85%). Even if the form is poorly bioavailable elemental zinc, the FEEDAP Panel considered it appropriate to introduce the following considerations regarding the safety of the excipient for the target species, the consumers, the user and the environment, as well as on its specification.

Safety for target animals. Concerning the bioavailability of the zinc source, Bennison et al. (2010a, b) reported that elemental zinc has about 30% bioavailability as compared to zinc oxide (of ZnO). The FEEDAP Panel has performed a calculation to estimate the contribution of the zinc contained in the bolus to the diet of cattle (400 kg bw, with an intake of 9.1 kg complete feed) and adult sheep (60 kg bw, with an intake of 1.36 kg complete feed), considering a background of zinc in feed of 40 mg/kg (EFSA FEEDAP Panel, 2014).

- Cattle:
  130 g bolus/180 days = 0.72 g/day; considering 82.96% is Zn→ 0.597 g/day → 66 mg Zn/kg complete feed
- Adult sheep:
  48 g bolus/180 days = 0.267 g/day; considering 84.56% is Zn → 0.225 g/day → 166 mg Zn/kg complete feed

The above estimate indicates that in the case of sheep the zinc contained within the bolus would lead to an exceedance of the maximum authorised zinc in feed (about 200 mg/kg, counting also the zinc background of the diet). Therefore, also considering that the animals receiving the boluses may meet their zinc needs already through the forage, the FEEDAP stresses its recommendation for a tailored design of the bolus to the weight of the animals.

Safety for consumers. As far as the maximum level of zinc delivered by the bolus is compatible with the maximum total authorised zinc content in complete feed, the safety for consumers would not be impacted.

Safety for users. The FEEDAP Panel has calculated the potential zinc released from the dust when handling/manufacturing the bolus, with an estimate of a maximum concentration of 254 mg Zn/m^3, and further on the respirable fraction of zinc from dust, which would be about 8.1 mg/m^3. Considering that the proposed TLV value for zinc of 2 mg/m^3 (ACGIH, 2003) is exceeded by more than four times, the zinc content of the bolus represents a risk to users by inhalation.

Safety for environment. Elemental zinc will likely be transformed in zinc oxide in the environment, so the assessment of the standard ionic zinc would apply. Therefore, as far as the maximum level of zinc delivered by the bolus is compatible with the maximum total authorised zinc content in complete feed, the safety for the environment would not be impacted.

Specification on particle size. The FEEDAP Panel notes that the above considerations apply only to a zinc ballast product in which particles are within a bulk standard size, i.e. containing no nanoparticles (≤ 100 nm in size) or small-sized particles retaining properties that are characteristic of the nanoscale (EFSA Scientific Committee, 2018). In this context, the FEEDAP Panel stresses the need of specifications for the particle size distribution of the zinc elemental ballast, when used as an excipient in the bolus manufacture.

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