SCIENTIFIC OPINION

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Safety and efficacy of selenium compounds (E8) as feed additives for all animal species: sodium selenite, based on a dossier submitted by Todini and Co SpA

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)

Abstract

Selenium is an essential trace element for vertebrates, involved in a series of vital metabolic functions. Sodium selenite is a safe and efficacious source of selenium for all animal species/categories. The use of sodium selenite as a source of selenium in animal nutrition is safe for the consumer, provided that the total maximum authorised content of selenium in complete feed is respected. The additive is an irritant to the skin, eyes and mucosae, whereas it is not a skin sensitiser. Systemic exposure to selenium could result from dermal contact. Users/workers handling the additive would be exposed to selenium by inhalation at levels which constitute a risk. The use of sodium selenite in animal nutrition up to the maximum authorised content in feed would not raise concerns to the environment.

Keywords: nutritional additive, compounds of trace elements, selenium, sodium selenite, safety, environment, efficacy

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Summary

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 and efficacy of selenium compounds as feed additive for all animal species: sodium selenite, based on a dossier submitted by Todini Vital Chemicals S.P.A.

Selenium is a trace element that is essential for vertebrates and is involved in a series of vital metabolic functions (e.g. prevention of oxidative stress, proper thyroid function, maintenance of cellular redox status, immunocompetence, detoxification of heavy metals and xenobiotics).

Sodium selenite is a safe source of selenium for all animal species/categories.

The use of sodium selenite as a source of selenium in animal nutrition is safe for the consumer, provided that the total maximum authorised content of selenium in complete feed is respected.

The additive is an irritant to the skin, eyes and mucosae, whereas it is not a skin sensitiser. Systemic exposure to selenium could result from dermal contact. Users/workers handling the additive would be exposed to selenium by inhalation at levels which constitute a risk.

The use of sodium selenite in animal nutrition up to the maximum authorised content in feed would not raise concerns to the soil compartment, the ground or surface water. Concerning marine sediments, given the standard aquaculture practices and the low potential maximum concentration of selenium from fish feeds, any impact on the environment is unlikely.

Sodium selenite is an efficacious source of the essential trace element selenium for all animal species/categories.

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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 10(2) of that Regulation also specifies that for existing products within the meaning of Article 10(1), an application shall be submitted in accordance with Article 7, at the latest one year before the expiry date of the authorisation given pursuant to Directive 70/524/EEC for additives with a limited authorisation period, and within a maximum of seven years after the entry into force of this Regulation for additives authorised without a time limit or pursuant to Directive 82/471/EEC.

The European Commission received a request from Todini Vital Chemicals S.P.A.[2] for re-evaluation of authorisation of selenium-containing additive, *sodium selenite*, when used as feed additive for all animal species (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 10(2) (re-evaluation of an authorised 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 21 October 2014.

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 selenite, when used under the proposed conditions of use (see Section 3.1.7.).

1.2. Additional information

Selenium is a trace element, which is essential for vertebrates and is involved in a series of vital metabolic functions (e.g. prevention of oxidative stress, proper thyroid function, maintenance of cellular redox status, T-cell immunity, detoxification of heavy metals and xenobiotics, calcium homeostasis, skeletal and cardiac muscle metabolism, including metabolism of lipids such as arachidonic and linoleic acids, cholesterol and its esters). The biological role of selenium and the symptoms of deficiency and toxicity in farm animals and humans were described in EFSA previous opinions of the FEEDAP (EFSA, 2006) and of the NDA (EFSA NDA Panel, 2014) Panels. The FEEDAP Panel considered also a recently published book on selenium (Preedy, 2015) and found that there is no additional relevant information which would modify the EFSA previous opinions.

The additive "Sodium selenite" 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]

The FEEDAP Panel has already adopted two opinions on sodium selenite in the frame of re-evaluation (EFSA FEEDAP Panel, 2015, 2016).

A compilation of risk assessments carried out on selenium and its compounds, including opinions from EFSA Panels other than the FEEDAP Panel, is in Appendix A. A list of authorisations of selenium compounds in the EU, other than as feed additive, is reported in Appendix B.

[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] Todini Vital Chemicals S.P.A. Corso Milano, 46. I-20052 Monza (MI), Italy. Following a communication from the applicant, received on 9 December 2014, the name of the company changed to Todini and Co SpA.
[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

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[5] in support of the authorisation request for the use of sodium selenite as a feed additive. The technical dossier was prepared following the provisions of Article 7 of Regulation (EC) No 1831/2003, Regulation (EC) No 429/2008[6] and the applicable EFSA guidance documents.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, peer-reviewed scientific papers and other scientific reports, to deliver the present output.

EFSA commissioned the University of Gent (Belgium) and the University Rovira i Virgili (Spain) to carry out studies of selected trace and ultratrace elements, and on the bioavailability interactions and incompatibilities of trace elements, respectively. The findings were submitted to EFSA in the form of technical reports (Van Paemel et al., 2010; Cano-Sancho et al., 2014); both reports included selenium. Information from these reports has been used in this opinion.

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of sodium selenite in animal feed. The Executive Summary of the EURL report can be found in the Annex.[7]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of sodium selenite is in line with the principles laid down in Regulation (EC) No 429/2008[8] 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, 2008a), Guidance for the preparation of dossiers for the re-evaluation of certain additives already authorised under Directive 70/524/EEC (EFSA, 2008b), 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), 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 selenite for use in feed for all animal species/categories; it is already authorised in the EU as a nutritional feed additive and foreseen for re-evaluation. This inorganic compound is already authorised in the EU as nutritional feed additive and has been used in animal nutrition as a source of the essential trace element selenium for decades. 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.

3.1. Characterisation

For compounds of trace elements, the activity of the element itself is considered.

[5] FEED dossier reference: FAD-2010-0362.

[6] 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.

[7] The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/default/files/finrep-fad-sodium_selenite_group.pdf

[8] Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

3.1.1. Characterisation and identity

Sodium selenite (International Union of Pure and Applied Chemistry (IUPAC) name disodium selenite; other names: selenious acid disodium salt, sodium selenium oxide, disodium selenium trioxide) is identified by Chemical Abstracts Service (CAS) number 10102-18-8 and the European Inventory of Existing Commercial chemical Substances (EINECS) number 233-267-9. Sodium selenite has the chemical formula Na_2SeO_3 (molecular weight 172.94 Da, theoretical maximum selenium content 45.7 %). The structural formula is given in Figure 1.

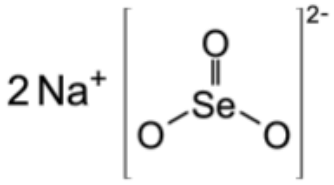

Figure 1: Structural formula of sodium selenite.

The additive contains by specification ≥ 45 % selenium. The applicant provided analytical data of six batches of the additive showing a selenium content within a range of 45.1 to 45.5 %.[9,10]

The applicant stated that the additive is marketed for incorporation into feedingstuffs as a premixture containing 1 or 4.5 % selenium from sodium selenite.

3.1.2. Impurities

Levels of lead, cadmium, arsenic and mercury contents in eight batches were <3, <1, <5 and <1 mg/kg, respectively; nickel (five batches) was <0.1mg/kg; fluorine (three batches) was ≤300 mg/kg.[11] Tellurium (five batches) was up to 34 mg/kg product. These levels are compliant with the thresholds set in Directive 2002/32/EC[12] for compounds of trace elements or, if not mentioned in the Directive, do not represent a concern.

Levels of dioxins and the sum of dioxins and dioxin-like polychlorinated biphenyls (PCBs) measured in three batches were ≤ 0.05 ng WHO-PCDD/F-TEQ/kg and ≤ 0.1 ng WHO-PCDD/F-PCB-TEQ/kg,[13] thus complying with the requirements of the EU legislation.

3.1.3. Physical state of the product

The product is a white crystalline powder. It is highly soluble in water (461 g/L at 19.5 ºC), its melting point is 710 ºC. The pH varies between 9 and 10 in a 1 % aqueous solution.[14] The bulk density is 1300 kg/m^3.[15]

Particle size distribution was measured by laser diffraction in three batches showing that particles <10 µm were in the range of 10.1–22.3%, particles <50 µm ranged from 67.2 to 76.0 % and particles <100 µm from 82.8 to 90.1% (v/v).[16,17] The dusting potential of three batches was analysed according to the Stauber–Heubach method; the calculated values were 0.5, 7.8 and 20.2 g/m^3.[18,19]

[9] Technical Dossier/Section II/Annex II_2.1.3.a.
[10] Technical dossier/Supplementary information September 2015.
[11] Technical Dossier/Section II/Annex II_2.1.4.a.
[12] 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.
[13] Technical Dossier/Section II/Annex II_2.1.4.c.
[14] Technical Dossier/Section II.
[15] Technical Dossier/Section II/Annex II_2.1.5.b.
[16] Technical Dossier/Section II/Annex II_2.1.5.a.
[17] Technical dossier/Supplementary information September 2015.
[18] Technical dossier/SectionII/Annex II_2.1.5.c.
[19] Technical dossier/Supplementary information September 2015.

3.1.4. Manufacturing process

Sodium selenite is manufactured by reacting selenium with oxygen to produce selenium dioxide, which is then dissolved in water and neutralised with sodium hydroxide to produce sodium selenite. The sodium selenite solution is decolourised, sodium selenite is crystallised and recovered by evaporation and centrifugation. The resulting sodium selenite is finally dried and milled.[20]

3.1.5. Stability and homogeneity

Stability data are not required for inorganic compounds of trace elements.

The potential of the additive to distribute homogeneously was examined on a mash feed for pigs for fattening based on wheat, barley, soybean meal with an analysed background selenium content of 0.06 mg/kg. Feed was supplemented with 0.4 mg Se/kg from a 1 % Se-containing premixture of sodium selenite and dolomite as carrier. The selenium content of nine feed subsamples showed a coefficient of variation 9.6 %.[21]

3.1.6. Physico-chemical incompatibilities in feed

No incompatibilities resulting from the use of sodium selenite in compound feed are expected with the feed materials, carriers, other approved additives or medicinal products.

3.1.7. Conditions of use

Sodium selenite is intended to be used as a source of the trace element selenium for all animal species and categories up to a maximum total content of 0.5 mg Se/kg complete feed. The applicant recommends that, in order to obtain homogeneous distribution of the additive in compound feed, the additive should be incorporated in the final feed via a premixture.[22]

3.2. Safety

3.2.1. Safety for the target species

Symptoms of deficiency and toxicosis of selenium are described in detail in previous opinions of the FEEDAP Panel (EFSA, 2006; EFSA FEEDAP Panel, 2011b, 2015, 2016) and scientific reviews (e.g. McDowell, 2003; Suttle, 2010).

Tolerance studies are not required for compounds of trace elements already authorised. The National Research Council (NRC, 2005) published the following maximum tolerable levels (MTLs): 5 mg Se/kg feed dry matter (DM) for cattle and sheep, 4 mg Se/kg feed DM for pigs, 3 mg Se/kg feed DM for poultry. The MTLs for horses and fish were derived from interspecies extrapolation and amount to 5 and 2 mg Se/kg DM feed, respectively. The NRC could not set MTLs for dogs and cats.

The applicant provided a literature review on the effects of feed supplementation with sodium selenite for several animal species covering the years 2000 to present (database search CAB Abstracts).[23] The most relevant studies found in this review for ruminants, poultry and pet animals were already summarised in an opinion recently delivered by the FEEDAP Panel on sodium selenite and are considered as valid (EFSA FEEDAP Panel, 2016). Other studies not mentioned so far do not add relevant new information. In addition, the applicant provided also studies in fish, published after the NRC publication, which are summarised below.

Fish

Juvenile black seabream (*Acathopagrus schlegeli*), initial body weight: 7.0±0.1 g bw, 10 per group, were fed sodium selenite-supplemented diets containing 0.21, 0.30, 0.52, 1.29 or 12.3 mg Se/kg diet for 15 weeks (Lee et al., 2008). No difference in survival rate was found. Only the group with 12.3 mg Se/kg diet showed a final lower weight gain and higher feed/gain ratio than those fed the other diets.

[20] Technical Dossier/Section II.
[21] Technical dossier/Supplementary information September 2015.
[22] Technical Dossier/Section II.
[23] Technical dossier/Supplementary information September 2015.

Although no differences in haematocrit (PCV), haemoglobin (Hb) and red blood cells (RBC) were found, there was a tendency for lower PCV, Hb and RBC values in the 12.3 mg Se/kg group, in which also histopathological lesions (tubular necrosis and polycystic dilation of tubules in the kidney tissues) were found. Considering the weaknesses of the study (no replicates, low number of animals), the only conclusion that could be drawn is that a dietary concentration of 12.3 mg Se/kg is toxic to juvenile black seabream.

Jaramillo et al. (2009) studied the effects (weight gain, feed/gain ratio and mortality) of graded levels of dietary selenium from sodium selenite in juvenile hybrid striped bass (*Morone chrysops* × *M. saxatilis*) for 12 weeks. The data allow the conclusion that dietary selenium (i) up to 5 mg/kg would apparently be tolerated and (ii) about 20 mg/kg is toxic.

The studies described above are not considered suitable to modify the MTL given by the NRC.

Conclusions on the safety for the target species

The MTLs for dietary selenium established in the literature are markedly above the currently authorised maximum content for total selenium in complete feed (0.5 mg Se/kg). Within that range, sodium selenite is considered to be a safe source of selenium for all animal species/categories.

3.2.2. Safety for the consumer

Absorption, distribution, metabolism and excretion of selenium have been already described in the Opinions of the FEEDAP Panel (EFSA, 2006) and the NDA Panel (EFSA NDA Panel, 2014).

Metabolic and residue studies

The deposition of selenium and speciation of its compounds in edible tissues and products of animal origin is related to different metabolism of inorganic and organic selenium sources used as feed additives. When sodium selenite is given as supplement to feed animals, the selenite anion is, after being absorbed, taken up rapidly by erythrocytes and reduced by glutathione into dihydrogen selenide (H_2Se) within a very short time. After efflux into plasma, H_2Se is bound to albumin and transported to the liver for the synthesis of selenoprotein P and subsequently of other specific selenoproteins (Kobayashi et al., 2001). Selenium in the structural centre of specific selenoproteins occurs in the form of selenocystein (SeCys), which is synthesised from H_2Se via selenophosphate and activated serine (Ser) residue on ^{SeCys}tRNA (Ser ^{SeCys}tRNA) to SeCys ^{SeCys}tRNA, but not directly from free SeCys (Suzuki, 2005). Consequently, the predominant selenium species in edible tissue and products of animals fed diets supplemented with inorganic selenium sources is SeCys incorporated into specific selenoproteins. On the other hand, in animals fed diets enriched with organic selenium sources based on selenomethionine (SeMet), a significant non-specific incorporation of SeMet, particularly into general proteins of milk and muscle, also occurs (Phipps et al., 2008; Juniper et al., 2008, 2009, 2011). It is well known that SeMet cannot be synthesised in the body by mammals, birds and fish. There is experimental evidence that animals fed diets supplemented with organic selenium based on SeMet sources show a considerably higher selenium deposition in edible tissue/products than animals given inorganic selenium (see also EFSA FEEDAP Panel, 2011b).

No data on tissue/product deposition of selenium specific to the feed additive under assessment were submitted by the applicant. However, based on the available published literature, the FEEDAP Panel identified a total selenium concentration and/or its range in muscle, liver, kidney, eggs and milk when sodium selenite (as such, not formulated) was supplemented to animal feed providing levels between 0.3 and 0.5 mg Se/kg feed (Table 1). When original data were available on a dry matter basis only, the selenium concentration on fresh weight basis was calculated using foodstuff tables published by Souci et al. (2008).

Table 1: Selenium concentration in edible tissues, eggs and milk (on fresh weight basis) from animals fed diets supplemented with sodium selenite between 0.3 and 0.5 mg Se/kg.

Tissues and products	Animal species and/or categories					
	Pigs for fattening[(a)]	Chickens for fattening[(b)]	Turkeys[(c)]	Ruminants	Laying hens	Fish[(d)]
Muscle (mg/kg)	0.10–0.20	0.04–0.17	0.26	0.09–0.14[(e)]	–	0.15–0.82
Liver (mg/kg)	0.42–0.68	0.30–0.70	0.49	0.45– 0.50[(e)]	–	
Kidney (mg/kg)	1.23–3.74	0.30–1.95	0.92	1.43–3.70[(e)]	–	
Milk (µg/L)	–	–	–	11.80–19.70[(f)]	–	
Egg (mg/kg)	–	–	–	–	0.15–0.30[(g)]	

(a): Based on: Mahan and Parrett, 1996; Mahan et al., 1999; Mateo et al., 2007; Svoboda et al., 2009; Kawecka et al., 2013; Jlali et al., 2014.
(b): Based on: Payne and Southern, 2005; Skřivan et al., 2008; Petrovic et al., 2010; Hu et al., 2012; Ryzner et al., 2013; Chen et al., 2013; Briens et al., 2014.
(c): Based on: Juniper et al., 2011.
(d): Based on: Souci et al., 2008; Kouba et al., 2014.
(e): Based on: Juniper et al., 2008 (cattle for fattening), 2009; Gresakova et al., 2013 (lambs).
(f): Based on: Aspila, 1991; Syrjala and Aspila, 1993; Ortman and Pehrson, 1999; Knowles et al., 1999; Gierus et al., 2002; Brzoska, 2004; Slavik et al., 2008; Ceballos et al., 2009; Meyer et al., 2014.
(g): Based on: Paton et al., 2002; Payne et al., 2005; Utterback et al., 2005; Skřivan et al., 2006; Pan et al., 2007; Pavlovic et al., 2009; Cobanová et al., 2011; Surai and Fisinin, 2014.

Toxicological studies

No specific toxicological studies for product under assessment were provided.

The toxicology of selenium salts, including sodium selenite, has been extensively reviewed by the EU Scientific Committee on Food (SCF) (EC, 2000), the Agency for Toxic Substances and Disease Registry (ATSDR, 2003), the WHO (2011), the European Medicines Agency (EMA, 2015), and particularly for genotoxic effects by Cemeli et al. (2006) and Valdiglesias et al. (2010). Maggio et al. (2010) and, more recently, Ren et al. (2016) have also studied some related toxic effects of selenium.

In summary, the following conclusions can be drawn from the cited sources:

- Selenosis is a well-known disease in humans and animals.[24] In humans, it results from acute (e.g. 250 mg Se as a single dose) or chronic selenium toxicity (no observed adverse effect level (NOAEL) of 850 µg Se/day) (EC, 2000). Other related toxic effects in humans are disruption of endocrine function and an increased synthesis of thyroid (T3) and growth hormones (Valdiglesias et al., 2010). In addition, selenium may increase the levels of insulin-like growth factor in humans (Maggio et al., 2010); in mice, such effect is associated with altered bone homeostasis at high selenium doses (Ren et al., 2016). Nevertheless, these effects were reversible and disappeared in adult individuals as soon as the intake of toxic selenium doses was stopped.
- The genotoxic and antigenotoxic properties of sodium selenite, sodium selenate and selenous acid are highly dependent on the conditions under which they are evaluated (Cemeli et al., 2006), and could be related to changes in the equilibrium between pro-oxidant to antioxidant conditions. *In vitro* studies indicate that the genotoxic effects of selenium salts are associated with the production of reactive oxygen species, and that glutathione promotes these reactions. However, these effects could be shown *in vivo* only when toxic doses were applied (EC, 2000).
- The only selenium compound shown to be carcinogenic in animals is selenium sulphide. However, this compound is chemically different (insoluble in water) from the organic and inorganic forms for use in food, feed and the environment (ATSDR, 2003).
- Selenium at doses higher than 15 mg/kg in the diet of birds (Spallholz and Hoffman, 2002) and than 3 mg/kg in the diet of fish (Lemly, 2002) is teratogenic; findings on developmental toxicity in mammals are controversial (EC, 2000; ATSDR, 2003; WHO, 2011; EMA, 2015).

[24] For clinical symptoms of selenosis see: EFSA, 2006; Suttle, 2010; EFSA NDA Panel, 2014.

Assessment of consumer safety

The EU SCF (EC, 2000) established 300 µg Se/day as Tolerable Upper Intake Level (UL) for adults (including pregnant and lactating women). This figure was based on the NOAEL of 850 µg Se/day for clinical selenosis in the study on 349 subjects carried out by Yang et al. (1989), and followed up in the study by Yang and Zhou (1994) on five individuals who recovered from selenosis (when their intake had been reduced to a mean of 819 µg Se/day), and applying an uncertainty factor of 3. As there were no data to support a derivation of a UL for children, the SCF (EC, 2000) extrapolated the UL from adults to children on the basis of reference body weights. The proposed UL values range from 60 µg/day (1–3 years) to 250 µg selenium/day (15–17 years).

In a recent opinion on Dietary References Values (DRV) for selenium (EFSA NDA Panel, 2014), the estimated average selenium intakes in the EU for children aged from 1 to < 3 years and adults (≥ 18 years) ranged from 17 to 36 µg Se/day and from 31 to 66 µg Se/day, respectively. These figures also include selenium intake from food of animal origin.

Based on selenium deposition data in animal tissues/products obtained by reviewing available published literature (see Section 3.2.1), the FEEDAP Panel made an assessment of consumer exposure to selenium when sodium selenite was used as feed additive up to the maximum authorised selenium level in feed. For total selenium concentrations in tissue/products of animal origin, the higher values found in various edible tissues and products were used. The food basket and its application, as described in the FEEDAP Guidance on consumer safety (EFSA FEEDAP Panel, 2012c), were used to make a conservative estimate of the intake of selenium by adults and toddlers from animal tissues/products following supplementation of the feed with sodium selenite (Table 1). The results (Tables 2 and 3) show that daily intake of selenium from two food items of animal origin contributing to the highest selenium exposure would be below the ULs for both adults and toddlers. Even with the addition of the selenium intake from the consumption of food items, without considering food of farmed animal origin – values being estimated as 60 and 10 µg/day for adults (EFSA, 2006) and toddlers (EFSA FEEDAP Panel, 2011b), respectively—the ULs for adults and toddlers will not be exceeded.

Table 2: Selenium exposure in adults (mg/day) consuming tissues/products from animals fed diets supplemented with 0.3–0.5 mg Se/kg feed from sodium selenite.

Food	Amount consumed (kg/day)	Food Se content (mg/kg)	Se intake (mg/day)
Meat	0.290	0.260	0.075
Kidney	0.015	3.740	0.056
Total (mg/day)			0.131

Table 3: Selenium exposure in toddlers (mg/day) consuming tissues/products from animals fed diets supplemented with 0.3–0.5 mg Se/kg feed from sodium selenite.

Food	Amount consumed (kg/day)	Food Se content (mg/kg)	Se intake (mg/day)
Meat	0.090	0.260	0.023
Milk	1.050	0.020	0.021
Total (mg/day)			0.044

Conclusions on the safety for the consumer

Based on extensive published literature data, the use of sodium selenite as a source of selenium in animal nutrition is considered to be safe for the consumer, provided that the total maximum authorised content of selenium in complete feed is respected.

3.2.3. Safety for the user

The occupational safety of selenium compounds has been reviewed by the International Programme on Safety (IPCS, 1987) and by the ATSDR (2003). Selenium compounds are recognised as highly toxic by inhalation, ingestion and skin contact.

The applicant also provided a document related to safety for users/workers with some information extracted from the CSR (Chemical Safety Report) created under REACH for registration of sodium selenite.[25]

Effects on the respiratory system

No specific data have been provided by the applicant. Threshold limit values (TLV) for selenium compounds, calculated as selenium, ranging between 0.02 and 0.2 mg/m^3, have been set by different committees (e.g. Deutsche Forschungsgemeinschaft (DFG) which sets the Maximale Arbeitsplatz Konzentration (MAK) List; Occupational Safety and Health Administration (OSHA); National European Authorities). The lowest value of 0.02 mg/m^3 was identified by the DFG.

The dusting potential of sodium selenite varied between 0.5 and 20.2 g/m^3, with 10–22% particles of respirable size. No selenium concentration data in sodium selenite dust were available. Thus, taking into account that sodium selenite contains by specification ≥ 45 % selenium, a concentration of selenium between 23 and 2000 mg/m^3 is estimated in the dust. These estimated values exceed by several orders of magnitude the MAK value as well as other less conservative TLV. Consequently, the FEEDAP Panel considers that the additive poses a health risk upon inhalation.

Effects on the eyes and skin

Two *in vitro* studies on eye irritation (according to OECD Guideline 437)[26] and on skin irritation (according to OECD Guideline 439)[27] were included in the CSR. The results showed that the additive can be considered as an irritant for skin and mucosae. A further *in vitro* study on skin corrosion (according to OECD Guideline 431)[28] did not show a corrosive potential. Moreover, cutaneous absorption of selenium is recognised to occur after skin contact causing systemic exposure (ATSDR, 2003). Selenium compounds are generally known to be skin sensitisers (US EPA, 2000; ATSDR, 2003). However, results from two *in vivo* local lymph node assays (according to OECD Guideline 429)[29] conducted on mice presented in the CSR did not identify a skin sensitisation potential. In particular one study did yield ambiguous results, (Stimulation Index (SI)[30] scores ranging 2.0–3.2), likely due to local inflammatory reactions elicited by the intradermal injection of the additive; on the contrary, the other study was fully negative (SI range 0.41–1.05). A clinical case study carried out in 1988, available only as an abstract, could not be evaluated due to the limited information reported (Senff et al., 1988).

Conclusions on the safety for users/workers

The additive is considered to be an irritant to the skin, eyes and mucosae, whereas it is not a skin sensitiser. Systemic exposure to selenium could result from dermal contact. Users/workers handling the additive would be exposed to selenium by inhalation at levels which constitute a risk.

3.2.4. Safety for the environment

Based on the conservative calculation method provided in the technical guidance for assessing the safety of feed additives for the environment (EFSA, 2008a), addition of sodium selenite to animal feed at a concentration of 0.5 mg Se/kg complete feed would maximally result in addition of 10.7 µg Se/kg soil after a 1-year application of manure, assuming that 100 % of the dose will be excreted. This addition is small compared with the background concentration of selenium in soil which is, on a global average, of 330 µg Se/kg. There are currently no EU Environmental Quality Standards (EQSs) for selenium in soil, but the Netherlands has a long-term target value of 700 µg Se/kg dry weight (dw) (Warmer and van Dokkum, 2002) and the Canadian Council of Ministers of the Environment (CCME) has derived a Soil Quality Guideline for agricultural and residential/parkland use of 1,000 µg/kg

[25] Technical dossier/Supplementary information September 2015.
[26] "Bovine corneal opacity and permeability test"
[27] "In vitro skin irritation on reconstructed human epidermis model"
[28] "In vitro corrosion on human skin model"
[29] "Skin Sensitisation. Local Lymph Node Assay"
[30] The endpoint stimulation index (SI) gives a ratio of thymidine incorporation in lymph nodes from dosed animals compared to the incorporation in lymph nodes from vehicle-treated control animals. The test is positive when the SI is greater than 3 for any of the dose concentrations.

(CCME, 2009). As the addition of selenium to soils from feed additives is small compared with background concentrations and regulatory limits (where in place), sodium selenite in feeds for terrestrial farm animals is considered safe to the soil compartment. Using the same reasoning, there would also be no concern for the ground or surface water compartments resulting from this application.

Using its technical guidance for assessing the safety of feed additives for the environment (EFSA, 2008a), the FEEDAP Panel calculated the worst-case concentrations in the environment resulting from the supplementation of fish feeds with sodium selenite at a total level of 0.5 mg Se/kg. In applications for land-based aquaculture operations, the surface water effluent from the fish farm is considered to be the most vulnerable compartment (EFSA, 2008a). The Predicted Environmental Concentration in surface water (PECswaq) was calculated to be at maximum 0.0013 µg/L, which is more than two orders of magnitude below the trigger value and therefore no further assessment is required for this particular aspect. When fed to fish in sea cages, the sediment under the cage is considered the compartment of concern (EFSA, 2008a). The PECsed was calculated to be 106 µg/kg wet weight, which exceeds the threshold for Phase I assessment (10 µg/kg). The conservative estimate of 106 µg Se/kg wet weight which could result from the use of sodium selenite in marine fish feed is lower than the lowest published sediment quality criterion (700 µg/kg; Warmer and van Dokkum, 2002). As the location of fish cages rotates on a regular basis, build-up of selenium in the sediment from sodium selenite added to fish feed is unlikely. Given the low theoretical maximum concentration of selenium in marine sediments resulting from selenium in fish feeds, it is unlikely that the use of sodium selenite as a feed additive would have any impact on the marine environment.

The FEEDAP Panel concludes that the use of sodium selenite in animal nutrition up to the maximum authorised content in feed would not raise concerns to the soil compartment, the ground or surface water. Concerning marine sediments, given the standard aquaculture practices and the low potential maximum concentration of selenium from fish feeds, any impact on the environment is unlikely.

3.3. Efficacy

Sodium selenite has been used in animal nutrition as a source of the essential trace element selenium for decades. Its efficacy (based on response in blood/serum and liver selenium levels, and in glutathione peroxidase activity in blood/plasma) is well documented in the scientific literature for swine (Mahan and Parrett, 1996), poultry (Kuricova et al., 2003) and bovine (Ortman and Pehrson, 1999).

The FEEDAP Panel concludes that sodium selenite is an efficacious source of the essential trace element selenium for all animal species/categories.

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[31] and good manufacturing practice.

4. Conclusions

Sodium selenite is a safe source of selenium for all animal species/categories.

The use of sodium selenite as a source of selenium in animal nutrition is safe for the consumer, provided that the total maximum authorised content of selenium in complete feed is respected.

The additive is an irritant to the skin, eyes and mucosae, whereas it is not a skin sensitiser. Systemic exposure to selenium could result from dermal contact. Users/workers handling the additive would be exposed to selenium by inhalation at levels which constitute a risk.

The FEEDAP Panel concludes that the use of sodium selenite in animal nutrition up to the maximum authorised content in feed would not raise concerns to the soil compartment, the ground or surface

[31] 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.

water. Concerning marine sediments, given the standard aquaculture practices and the low potential maximum concentration of selenium from fish feeds, any impact on the environment is unlikely.

Sodium selenite is an efficacious source of the essential trace element selenium for all animal species/categories.

Documentation provided to EFSA

1. Dossier Sodium selenite. October 2010. Submitted by Todini Vital Chemicals S.P.A.

2. Dossier Sodium selenite. Supplementary information. September 2015. Submitted by Todini Vital Chemicals S.P.A.

3. Evaluation report of the European Union Reference Laboratory for Feed Additives on the Methods(s) of Analysis for Sodium selenite.

4. Comments from Member States.

References

Aspila P, 1991. Metabolism of selenite, selenomethionine and feed-incorporated selenium in lactating goats and dairy cows. Journal of Agricultural Science in Finland, 63, 1–74.

ATSDR (Agency for Toxic Substances and Disease Registry), 2003. Toxicological profile for Selenium. US Department of Health and Human Services. Available online: http://www.atsdr.cdc.gov/toxprofiles/tp92.pdf

Briens M, Mercier Y, Rouffineau F, Mercerand F and Geraert PA, 2014. 2-Hydroxy-4-methylselenobutanoic acid induces additional tissue selenium enrichment in broiler chickens compared with other selenium sources. Poultry Science, 93, 85–93.

Brzoska F, 2004. Effect of calcium salts of fatty acids and selenium on cows' milk yield and composition. Annals of Animal Science, 4, 69–78.

Cano-Sancho G, Rovira J, Perelló G, Martorell I, Tous N, Nadal M and Domingo JL, 2014. Extensive Literature Search on the bioavailability of selected trace elements in animal nutrition: Incompatibilities and interactions. External Scientific Report submitted to EFSA. Available online: http://www.efsa.europa.eu/en/supporting/pub/565e.htm

CCME (Canadian Council of Ministers of the Environment), 2009. Canadian Soil Quality Guidelines. SELENIUM. Environmental and Human Health Effects. Scientific Criteria Document. Canadian Council of Ministers of the Environment, Winnipeg, MB, Canada. Available online: http://www.ccme.ca/files/Resources/supporting_scientific_documents/soqg_se_scd_1438.pdf

Ceballos A, Sánchez J, Stryhn H, Montgomery JB, Barkema HW and Wichtel JJ, 2009. Meta-analysis of the effect of oral selenium supplementation on milk selenium concentration in cattle. Journal of Dairy Science, 92, 324–342.

Cemeli E, Marcos R and Anderson D, 2006. Genotoxic and antigenotoxic properties of selenium compounds in the in vitro micronucleus assay with human whole blood lymphocytes and TK6 lymphoblastoid cells. The Scientific World Journal, 6, 1202–1210.

Chen G, Wu J and Li C, 2013. Effect of different selenium sources on production performance and biochemical parameters of broilers. Journal of Animal Physiology and Animal Nutrition, 98, 747–754.

Cobanová K, Petrovic V, Mellen M, Arpásova H, Gresáková L and Faix S, 2011. Effects of dietary form of selenium on its distribution in eggs. Biological Trace Element Research, 144, 736–746.

EC (European Commission), 2000. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Selenium. Health and Consumer Protection Directorate-General, Brussels, Belgium. Available online: http://ec.europa.eu/food/fs/sc/scf/out80g_en.pdf

EFSA (European Food Safety Authority), 2006. Opinion of the Scientific Panel on Additives and

Products or Substances used in Animal Feed on the safety and efficacy of the product Sel-Plex® 2000 as a feed additive according to Regulation (EC) No 1831/2003. EFSA Journal 2006;4(5):348, 40 pp. doi:10.2903/j.efsa.2006.348

EFSA (European Food Safety Authority), 2008a. Technical Guidance for assessing the safety of feed additives for the environment Prepared by the Panel on Additives and Products or Substances used in Animal Feed. EFSA Journal 2008;6(10):842, 28 pp. doi:10.2903/j.efsa.2008.842

EFSA (European Food Safety Authority), 2008b. Guidance of the Scientific Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) for the preparation of dossiers for the re-evaluation of certain additives already authorised under Directive 70/524/EEC. EFSA Journal 2008;779;6(9), 9 pp. doi:10.2903/j.efsa.2008.779

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2011a. Technical guidance: Tolerance and efficacy studies in target animals. EFSA Journal 2011;9(5):2175, 15 pp. doi:10.2903/j.efsa.2011.2175

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2011b. Scientific Opinion on Safety and efficacy of Sel-Plex® (organic form of selenium produced by Saccharomyces cerevisiae CNCM I-3060) for all species. EFSA Journal 2011;9(4):2110, 52 pp. doi:10.2903/j.efsa.2011.2110

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 2012;10(1):2535, 14 pp. doi:10.2903/j.efsa.2012.2535

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012b. Guidance for the preparation of dossiers for additives already authorised for use in food. EFSA Journal 2012;10(1):2538, 4 pp. doi:10.2903/j.efsa.2012.2538

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012c. Guidance for establishing the safety of additives for the consumer. EFSA Journal 2012;10(1):2537, 12 pp. doi:10.2903/j.efsa.2012.2537

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012d. Guidance on studies concerning the safety of use of the additive for users/workers. EFSA Journal 2012;10(1):2539, 5 pp. doi:10.2903/j.efsa.2012.2539

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2015. Scientific Opinion on the safety and efficacy of selenium compounds (E8) as feed additives for all animal species: sodium selenite (coated granulated preparation), based on a dossier submitted by Doxal Italia S.p.A. EFSA Journal 2015;13(11):4271, 27 pp. doi:10.2903/j.efsa.2015.4271

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2016. Scientific Opinion on the safety and efficacy of selenium compounds (E8) as feed additives for all animal species: sodium selenite, based on a dossier submitted by Retorte GmbH Selenium Chemicals and Metals. EFSA Journal 2016;14(2):4398, 26 pp. doi:10.2903/j.efsa.2016.4398

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on Dietary Reference Values for selenium. EFSA Journal 2014;12(10):3846, 67 pp. doi:10.2903/j.efsa.2014.3846

EMA (European Medicines Agency), 2015. European public MRL assessment report (EPMAR) – potassium selenate (all food producing species), sodium selenate (all food producing species), sodium selenite (all food producing species). Committee for Veterinary Medicinal Products. Available online: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500185181

Gierus M, Schwarz FJ and Kirchgessner M, 2002. Selenium supplementation and selenium status of dairy cows fed diets based on grass, grass silage or maize silage. Journal of Animal Physiology and Animal Nutrition, 86, 74–82.

Gresakova L, Cobanova K and Faix S, 2013. Selenium retention in lambs fed diets supplemented with selenium from inorganic or organic sources. Small Ruminant Research, 111, 76–82.

Hu CH, Li YL, Xiong L, Zhang HM, Song J and Xia MS, 2012. Comparative effects of nano elemental selenium and sodium selenite on selenium retention in broiler chickens. Animal Feed Science and Technology, 177, 204–210.

IPCS (International Program on Chemical Safety), 1987. Environmental heath criteria 58 – selenium. IPCS INCHEM. Available online: http://www.inchem.org/documents/ehc/ehc/ehc58.htm

Jaramillo F Jr, Peng L and Gatlin DM III, 2009. Selenium nutrition of hybrid striped bass (*Morone chrysops* × *M. saxatilis*) biovailability, toxicity and interaction with vitamin E. Aquaculture Nutrition, 15, 160–165.

Jlali M, Briens M, Rouffineau F, Geraert PA and Mercier Y, 2014. Evaluation of the efficacy of 2-hydroxy-4-methylselenobutanoic acid on growth performance and tissue selenium retention in growing pigs. Journal of Animal Science, 91, 1745–1752.

Juniper DT, Phipps RH, Ramos-Morales E and Bertin G, 2008. Effect of dietary supplementation with selenium-enriched yeast or sodium selenite on selenium tissue distribution and meat quality in beef cattle. Journal of Animal Science, 86, 3100–3109.

Juniper DT, Phipps RH, Ramos-Morales E and Bertin G, 2009. Effects of dietary supplementation with selenium enriched yeast or sodium selenite on selenium tissue distribution and meat quality in lambs. Animal Feed Science and Technology, 149, 228–239.

Juniper DT, Phipps RH and Bertin G, 2011. Effect of dietary supplementation with selenium-enriched yeast or sodium selenite on selenium tissue distribution and meat quality in commercial-line turkeys. Animal, 5, 1751–1760.

Kawecka M, Jacyno E, Matysiak B, Kołodziej-Skalska A and Pietruszka A, 2013. Effects of selenium and vitamin E supplementation on selenium distribution and meat quality of pigs. Acta Agriculturae Scandinavica A: Animal Sciences, 63, 194–200.

Knowles SO, Grace ND, Wurms K and Lee J, 1999. Significance of amount and form of dietary selenium on blood, milk, and casein selenium concentrations in grazing cows. Journal of Dairy Science, 82, 429–437.

Kobayashi Y, Ogra Y and Suzuki KT, 2001. Speciation and metabolism of selenium injected with 82Se-enriched selenite and selenate in rats. Journal of Chromatography B, 760, 73–81.

Kouba A, Velíšek J, Stará A, Masojídek J and Kozák P, 2014. Supplementation with sodium selenite and selenium-enriched microalgae biomass show varying effects on blood enzymes activities, antioxidant response, and accumulation in common barbel (*Barbus barbus*). BioMed Research International, 2014, 408270.

Kuricova S, Boldizarova K, Gresakova L, Bobcek R, Levkut M and Leng L, 2003. Chicken selenium status when fed a diet supplemented with Se-yeast. Acta Veterinaria Brno, 72, 339–346.

Lee S, Lee JH and Bai SC, 2008. A Preliminary Study on Effects of Different Dietary Selenium (Se) Levels onGrowth Performance and Toxicity in Juvenile Black Seabream, *Acathopagrus schlegeli* (Bleeker). Asian-Australasian Journal of Animal Science, 21, 1794–1799.

Lemly AD, 2002. Selenium assessment in aquatic ecosystems: a guide for hazard evaluation and water quality criteria. Springer Verlag, New York, NY, USA, 89–100.

Maggio M, Ceda GP, Lauretani F, Bandinelli S, Dall'Aglio E, Guralnik JM, Paolisso G, Semba RD, Nouvenne A, Borghi L, Ceresini G, Ablondi F, Benatti M and Ferrucci L, 2010. Association of plasma selenium concentrations with total IGF-1 among older community-dwelling adults: the InCHIANTI study. Clinical Nutrition, 29, 674–677.

Mahan DC and Parrett NA, 1996. Evaluating the efficacy of selenium-enriched yeast and sodium selenite on tissue selenium retention and serum glutathione peroxidase activity in grower and finisher swine. Journal of Animal Science, 74, 2967–2974.

Mahan DC, Cline TR and Richert B, 1999. Effect of dietary levels of selenium enriched yeast and sodium selenite as selenium sources fed to growing-finishing pigs on performance, tissue selenium, serum glutathione peroxidase activity, carcass characteristics, and loin quality. Journal of Animal Science, 77, 2172–2179.

Mateo RD, Spallholz JE, Elder R, Yoon I and Kim SW, 2007. Efficacy of dietary selenium sources on growth and carcass characteristics of growing-finishing pigs fed diets containing high endogenous selenium. Journal of Animal Science, 85, 1177–1183.

McDowell LR, 2003. Minerals in animal and human nutrition. 2nd edn. Elsevier Science, Amsterdam, The Netherlands.

Meyer U, Heerdegen K, Schenkel H, Dänicke S and Flachowsky G, 2014. Influence of various selenium sources on selenium concentration in the milk of dairy cows. Journal of Consumer Protection and Food Safety, 9, 101–109.

NRC (National Research Council), 2005. Mineral tolerance of animals, second revised edn. The National Academies Press, Washington, DC, USA.

Ortman K and Pehrson B, 1999. Effect of selenate as a feed supplement to dairy cows in comparison to selenite and selenium yeast. Journal of Animal Science, 77, 3365–3370.

Pan C, Huang K, Zhao Y, Qin S, Chen F and Hu Q, 2007. Effect of selenium source and level in hen's diet on tissue selenium deposition and egg selenium concentrations. Journal of Agricultural and Food Chemistry, 55, 1027–1032.

Paton ND, Cantor AH, Pescatore AJ, Ford MJ and Smith CA, 2002. The effect of dietary selenium source and level on the uptake of selenium by developing chick embryos. Poultry Science, 81, 1548–1554.

Pavlovic Z, Miletic I, Jokic Ž and Šobajic S, 2009. The effect of dietary selenium source and level on hen production and egg selenium concentration. Biological Trace Element Research, 131, 263–270.

Payne RL and Southern LL, 2005. Comparison of inorganic and organic selenium sources for broilers. Poultry Science, 84, 898–902.

Payne RL, Lavergne TK and Southern LL, 2005. Effect of inorganic versus organic selenium on hen production and egg selenium concentration. Poultry Science, 84, 232–237.

Petrovic V, Nollet L and Kovac G, 2010. Effect of dietary supplementation of trace elements on the growth performance and their distribution in the breast and thigh muscles depending on the age of broiler chickens. Acta Veterinaria Brno, 79, 203–209.

Phipps RH, Grandison AS, Jones AK, Juniper DI, Ramos-Morales E and Bertin G, 2008. Selenium supplementation of lactating dairy cows: effects on milk production and total selenium content and speciation in blood, milk and cheese. Animal, 2, 1610–1618.

Preedy VR, 2015. Selenium: Chemistry, Analysis, Function and Effects, Royal Society of Chemistry, UK, 465 pp.

Ren G, Ali T, Chen W, Han D, Zhang L, Gu X, Zhang S, Ding L, Fanning S and Han B, 2016. The role of selenium in insulin-like growth factor I receptor (IGF-IR) expression and regulation of apoptosis in mouse osteoblasts. Chemosphere, 144, 2158–2164.

Ryzner M, Takacova J, Cobanova K, Placha I, Venglovska K and Faix S, 2013. Effect of dietary *Salvia officinalis* essential oil and sodium selenite supplementation on antioxidative status and blood phagocytic activity in broiler chickens. Acta Veterinaria Brno, 82, 43–48.

Senff H, Kuhlwein A, Bothe C, Hausen BM and Tillac J, 1988. Allergic contact dermatitis from selenite. Contact Dermatitis, 19, 73–74.

Skřivan M, Šimáně J, Dlouhá G and Doucha J, 2006. Effect of dietary sodium selenite, Se-enriched yeast and Se-enriched Chlorella on egg Se concentration, physical parameters of eggs and laying hen production. Czech Journal of Animal Science, 51, 163–167.

Skřivan M, Dlouhá G, Mašata O and Ševčíková S, 2008. Effect of dietary selenium on lipid oxidation, selenium and vitamin E content in the meat of broiler chickens. Czech Journal of Animal Science, 53, 306–311.

Slavik P, Illek J, Brix M, Hlavicova J, Rajmon R and Jilek F, 2008. Influence of organic versus inorganic dietary selenium supplementation on the concentration of selenium in colostrum, milk and blood of beef cows. Acta Veterinaria Scandinavica, 50, 1–6.

Souci SW, Fachmann W and Kraut H, 2008. Food composition and nutrition tables, 7th edn. Stuttgart: Medpharm Scientific Publishers. Stuttgart.

Spallholz JE and Hoffman DJ, 2002. Selenium toxicity: cause and effects in aquatic birds. Aquatic Toxicology, 57, 27–37.

Surai PF and Fisinin VI, 2014. Selenium in poultry breeder nutrition: An update. Animal Feed Science and Technology, 191, 1–15.

Suttle NF, 2010. Mineral nutrition of livestock, 4th edn. CAB International Wallingford and Cambridge, UK, 587 pp.

Suzuki KT, 2005. Metabolomics of selenium: Se metabolites based on speciation studies. Journal of Health Science, 51, 107–114.

Svoboda M, Salkova A, Fajt Z, Kotrbacek V, Ficek R and Drabek J, 2009. Efficacy of Se-enriched alga Chlorella spp. and Se-enriched yeast on tissue selenium retention and carcass characteristics in finisher pigs. Acta Veterinaria Brno, 78, 579–587.

Syrjala QL and Aspila P, 1993. Selenium fertilization in Finland: Effect on milk and beef production. Norwegian Journal of Agricultural Sciences, 11, 159–167.

US EPA (United States Environmental Protection Agency), 2000. Selenium Compounds. Available online: http://www3.epa.gov/airtoxics/hlthef/selenium.html

Utterback PL, Parsons CM, Yoon I and Butler J, 2005. Effect of supplementing selenium yeast in diets of laying hens on egg selenium content. Poultry Science, 84, 1900–1901.

Valdiglesias V, Pásaro E, Méndez J and Laffon B, 2010. In vitro evaluation of selenium genotoxic, cytotoxic, and protective effects: a review. Archives of Toxicology, 84, 337–351.

Van Paemel M, Dierick N, Janssens G, Fievez V and De Smet S, 2010. Selected trace and ultratrace elements: Biological role, content in feed and requirements in animal nutrition – Elements for risk assessment. Technical Report submitted to EFSA. Available online: http://www.efsa.europa.eu/en/supporting/pub/68e.htm

Warmer H and van Dokkum R, 2002. Water pollution control in the Netherlands: Policy and practice 2001. RIZA report 2022.009. Institute for Inland Water Management and Waste Water Treatment, Lelystad, The Netherlands. 77 pp. Available online: http://www.helpdeskwater.nl/algemene-onderdelen/serviceblok/english/water-quality/@1041/waterpollution/

WHO (World Health Organisation), 2011. Selenium in drinking-water – Background document for development of WHO Guidelines for Drinking-water Quality. Available online: http://www.who.int/water_sanitation_health/dwq/chemicals/selenium.pdf

Yang G and Zhou R, 1994. Further observations on the human maximum safe dietary selenium intake in a seleniferous area of China. Journal of Trace Elements and Electrolytes in Health and Disease, 8, 159–165.

Yang G, Zhou R and Yin S, 1989. Studies of safe maximal daily selenium intake in a seleniferous area in China. I. Selenium intake and tissue selenium levels of the inhabitants. Journal of Trace Elements and Electrolytes in Health and Disease, 3, 77–87.

Abbreviations

ATSDR	Agency for Toxic Substances and Disease Registry
bw	body weight
CAS	Chemical Abstracts Service
CCME	Canadian Council of Ministers of the Environment
CSR	Chemical Safety Report
DM	dry matter
DRV	Dietary References Values
dw	dry weight
EC	European Commission
EEC	European Economic Community
EMA	European Medicines Agency
EPA	Environmental Protection Agency
EINECS	European Inventory of Existing Commercial chemical Substances
EQS	Environmental Quality Standard
EURL	European Union Reference Laboratory
FEEDAP Panel	Panel on Additives and Products or Substances used in Animal Feed
Hb	haemoglobin
H_2Se	dihydrogen selenide
IPCS	International Programme on Safety
IUPAC	International Union of Pure and Applied Chemistry
MAK	Maximale Arbeitsplatz Konzentration
MTL	Maximum Tolerable Level
Na	sodium
NDA Panel	EFSA Panel on Dietetic Products, Nutrition and Allergies
NOAEL	No Observed Adverse Effect Level
No	number
NRC	National Research Council
O	Oxygen
OECD	The Organisation for Economic Co-operation and Development
OSHA	Occupational Safety and Health Administration
PCBs	polychlorinated biphenyls
PCDD	polychlorinated dibenzodioxin
PCV	haematocrit
PEC	Predicted Environmental Concentration
RBC	red blood cells
REACH	Registration, Evaluation, Authorisation and restriction of Chemicals

SCF	Scientific Committee on Food
Se	selenium
SeCys	selenocystein
SeMet	selenomethionine
Ser	serine
SI	Stimulation Index
TEQ	Toxic Equivalent Factor
TLV	Threshold Limit Value
tRNA	transfer ribonucleic acid
UL	Tolerable Upper Intake Level
WHO	World Health Organization

Appendix A – List of Risk Assessment Reports on selenium and selenium compounds

In addition to the reports cited in this Opinion, other risk assessments have been carried out by EU bodies, institutions and industry (see list below).

1. EC Committees Opinions

Report of the Scientific Committee on Food on the Revision of Essential Requirements of Infant Formulae and Follow-on Formulae. http://www.ec.europa.eu/food/fs/sc/scf/out199_en.pdf

2. EU Member States RARs

The Environmental Agency. UK. Contaminants in soil: updated collation of toxicological data and intake values for humans Selenium Better Regulation Science Programme Science report: SC050021. March 2009. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/291235/scho0309bpqo-e-e.pdf

Scientific Advisory Committee on Nutrition (SACN). SACN Position Statement on Selenium and Health. UK. May 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/339431/SACN_Selenium_and_Health_2013.pdf

3. EFSA–FEEDAP Panel Opinions

Safety and efficacy of the product SelPlex® 2000 as a feed additive according to Regulation (EC) No 1831/2003. Scientific Panel on Additives and Products or Substances used in Animal Feed. http://www.efsa.europa.eu/en/efsajournal/doc/348.pdf

Safety and efficacy of the product Selenium enriched yeast (*Saccharomyces cerevisiae* NCYC R397) as a feed additive for all species in accordance with Regulation (EC) No 1831/2003. Scientific Panel on Additives and Products or Substances used in Animal Feed. http://www.efsa.europa.eu/en/efsajournal/doc/430.pdf

Safety and efficacy of SELSAF (Selenium enriched yeast from *Saccharomyces cerevisiae* CNCM I-3399) as feed additive for all species. Scientific Panel on Additives and Products or Substances used in Animal Feed. http://www.efsa.europa.eu/en/efsajournal/doc/992.pdf

Safety and efficacy of selenium in the form of organic compounds produced by the selenium-enriched yeast *Saccharomyces cerevisiae* NCYC R645 (SelenoSource AF 2000) for all species. Scientific Panel on Additives and Products or Substances used in Animal Feed. http://www.efsa.europa.eu/en/efsajournal/doc/3797.pdf

Safety and efficacy of Sel-Plex® (organic form of selenium produced by *Saccharomyces cerevisiae* CNCM I-3060) for all species. Scientific Panel on Additives and Products or Substances used in Animal Feed. http://www.efsa.europa.eu/en/efsajournal/doc/2110.pdf

Safety and efficacy of selenium in the form of organic compounds produced by the selenium-enriched yeast *Saccharomyces cerevisiae* NCYC R646 (Selemax 1000/2000) as feed additive for all species. Scientific Panel on Additives and Products or Substances used in Animal Feed. http://www.efsa.europa.eu/en/efsajournal/doc/2778.pdf

Safety and efficacy of hydroxy-analogue of selenomethionine as feed additive for all species. Scientific Panel on Additives and Products or Substances used in Animal Feed.

Safety and efficacy of L-selenomethionine as feed additive for all animal species. Scientific Panel on Additives and Products or Substances used in Animal Feed. http://www.efsa.europa.eu/en/efsajournal/doc/3219.pdf

4. EFSA–ANS Panel Opinions

Inability to assess the safety of selenium amino acid chelate added for nutritional purposes as a source of selenium in food supplements and the bioavailability of selenium from this source based on the supporting dossier. Scientific Statement of the Panel on Food Additives and Nutrient Sources added to Food (ANS). http://www.efsa.europa.eu/en/efsajournal/doc/952.pdf

Selenious acid as a source of selenium added for nutritional purposes to food supplements. Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food. http://www.efsa.europa.eu/en/efsajournal/doc/1009.pdf

Se-methyl-L-selenocysteine added as a source of selenium for nutritional purposes to food supplements. Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food. http://www.efsa.europa.eu/en/efsajournal/doc/1067.pdf

L-selenomethionine as a source of selenium added for nutritional purposes to food supplements. Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food. http://www.efsa.europa.eu/en/efsajournal/doc/1082.pdf

Chromium(III)-, iron(II)- and selenium-humic acid/fulvic acid chelate and supplemented humifulvate added for nutritional purposes to food supplements. Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food. http://www.efsa.europa.eu/en/efsajournal/doc/1147.pdf

5. EFSA–AFC Panel Opinions

Selenium-enriched yeast as source for selenium added for nutritional purposes in foods for particular nutritional uses and foods (including food supplements) for the general population. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food. http://www.efsa.europa.eu/en/efsajournal/doc/766.pdf

6. EFSA–NDA Panel Opinions

Scientific Opinion on the substantiation of health claims related to selenium and protection of DNA, proteins and lipids from oxidative damage (ID 277, 283, 286, 1289, 1290, 1291, 1293, 1751), function of the immune system (ID 278), thyroid function (ID 279, 282, 286, 1289, 1290, 1291, 1293), function of the heart and blood vessels (ID 280), prostate function (ID 284), cognitive function (ID 285) and spermatogenesis (ID 396) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). http://www.efsa.europa.eu/en/efsajournal/doc/1220.pdf

Scientific Opinion on the substantiation of health claims related to selenium and maintenance of normal hair (ID 281), maintenance of normal nails (ID 281), protection against heavy metals (ID 383), maintenance of normal joints (ID 409), maintenance of normal thyroid function (ID 410, 1292), protection of DNA, proteins and lipids from oxidative damage (ID 410, 1292), and maintenance of the normal function of the immune system (ID 1750) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). http://www.efsa.europa.eu/en/efsajournal/doc/1727.pdf

Scientific Opinion on the substantiation of health claims related to a combination of lycopene, proanthocyanidins, vitamin C, vitamin E, selenium and beta-carotene and contribution to normal collagen formation (ID 1669) and protection of the skin from UV-induced damage (ID 1669) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). http://www.efsa.europa.eu/en/efsajournal/doc/2239.pdf

Scientific Opinion on the substantiation of a health claim related to a combination of lycopene, vitamin E, lutein and selenium and protection of the skin from UV-induced (including photo-oxidative) damage pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). http://www.efsa.europa.eu/en/efsajournal/doc/2890.pdf

Scientific Opinion on the substantiation of a health claim related to a combination of lycopene, vitamin E, lutein and selenium and "helps to prepare and activate tanning" pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). http://www.efsa.europa.eu/en/efsajournal/doc/3001.pdf

Scientific Opinion on Dietary Reference Values for selenium. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). http://www.efsa.europa.eu/en/efsajournal/doc/3846.pdf

Scientific Opinion on the substantiation of a health claim related to selenium and protection of DNA, proteins and lipids from oxidative damage pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). http://www.efsa.europa.eu/en/efsajournal/doc/3890.pdf

Appendix B – List of authorisations of selenium other than as feed additive

Sodium selenite is authorised for use in food as a food supplement (Regulation (EC) No 1170/2009)[32] and a substance which may be added to foods as mineral (Regulation (EC) No 1925/2006).[33] Sodium selenite is also authorised as a substance that may be added for specific nutritional purposes in foods (Commission Regulation (EC) No 953/2009).[34]

Regarding pharmacologically active substances and their classification regarding MRLs in foodstuffs of animal origin, sodium selenite listed in Table 1 of the Annex of Regulation 37/2010[35] as "Allowed substances, no MRL required".

Sodium selenite can be used for cosmetic purposes (Regulation (EC) No 1223/2009 of the European Parliament and of the Council).[36]

According to the Annex to Regulation (EC) No 432/2012[37] the following health claims can be made only for food which is at least a source of copper 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".

[32] 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.

[33] 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

[34] 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.

[35] 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.

[36] Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. OJ L 342, 22.12.2009, p. 59.

[37] 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, 25.05.2012, p. 1.

Annex - Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of Analysis for Sodium selenite

In the current applications authorisation is sought under article 10(2) for *sodium selenite* under the category/ functional group (3b) "nutritional additives"/"compounds of trace elements", according to the classification system of Annex I of Regulation (EC) No 1831/2003. Specifically, authorisation is sought for the use of the *feed additive* for all categories and species. According to two of the Applicants (FAD-2010-0104 and FAD-2010-0362) the *feed additive* is a white powder containing at least of 98% of *sodium selenite* (based on anhydrous weight), which corresponds to a minimum content of 45% *selenium* and 13% *sodium*. Applicant FAD-2010-0369 intends to market a film granulated preparation of *sodium selenite* containing a minimum of 1% of *total selenium*. All feed additives are intended to be incorporated into *feedingstuffs* through *premixtures* with a maximum level of 0.5 mg *total selenium* /kg feedingstuffs.

For the characterisation of *sodium selenite* in the *feed additive* containing at least 98% of *sodium selenite* Applicant FAD-2010-0362 submitted the European Pharmacopoeia Monograph 1677, where identification is based on specific reactions involving ascorbic acid, barium chloride and sodium ions; while quantification is based on redox titration with potassium iodide, sodium thiosulfate and iodine solutions.

For the quantification of *total selenium* in the feed additive containing at least 98% of *sodium selenite* Applicant FAD-2010-0104 submitted a single-laboratory validated method based on conversion of sodium selenite to selenium and its further quantification by gravimetry; while Applicant FAD-2010-0369 applied a quantification assay derived from the European Pharmacopoeia method - based on redox titration with potassium iodide and sodium thiosulfate.

Additionally, two alternative single-laboratory validated and further verified methods based on (1) inductively coupled plasma atomic emission spectrometry (ICP-AES) and (2) inductively coupled plasma mass spectrometry (ICP-MS) - submitted in the frame of the dossiers FAD-2009-0010 and FAD-2012-0042 - were previously evaluated and recommended by the EURL - in the frame of other selenium dossiers - for the quantification of *total selenium* in *feed additives*.

Based on the information available, the EURL recommends for official control the titrimetric method described in the European Pharmacopoeia and/or the equivalent gravimetric method submitted by the Applicant for the characterisation of the *feed additive* containing at least 98% of *sodium selenite*; while ICP-MS or ICP-AES methods are recommended to quantify *total selenium* in the film granulated preparation (*feed additive*).

For the quantification of *total sodium* in the *feed additive*, containing at least 98% of *sodium selenite*, the EURL recommends for the official control two internationally recognised ring-trial validated methods: (i) EN ISO 6869:2000, based on Atomic Absorption Spectrometry (AAS) after dissolving in hydrochloric acid; and (ii) EN 15510:2007, based on Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES) after dissolving in hydrochloric acid, for which relative precisions ranging from 4 to 27 % were reported.

For the quantification of *total selenium* in *premixtures* and *feedingstuffs* two Applicants (FAD-2010-0362 and FAD-2010-0369) suggested several CEN and AOAC methods, while the Applicant FAD-2010-0104 submitted the EN 16159:2012 method based on Hydride Generation Atomic Absorption Spectrometry (HGAAS) after microwave digestion with HNO3/H2O2. This method was already evaluated and recommended by the EURL in the frame of previous selenium dossiers.

Further testing or validation of the methods to be performed through the consortium of National Reference Laboratories as specified by article 10 (Commission Regulation (EC) No 378/2005) is not considered necessary.