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Scientific opinion on the safety of selenite triglycerides as a source of selenium added for nutritional purposes to food supplements

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Abstract

Following a request from the European Commission, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on selenite triglycerides as a novel food (NF) pursuant to Regulation (EU) 2015/2283, their safety when added for nutritional purposes to food supplements as a source of selenium and the bioavailability of selenium from this source, in the context of Directive 2002/46/EC. The proposed NF is the first lipophilic organic form of selenium so far described in the literature. It is composed by a mixture of individual Se-containing lipids which do not occur in nature. The Panel considers that the information provided on the composition of the NF does not allow a complete characterisation of the product. From the data provided to characterise the absorption, distribution, metabolism and excretion of the NF, it cannot be established in which chemical form Se is systemically available and if it can enter the functional Se body pool to fulfil Se physiological functions. The Panel considers that, since it is not demonstrated that the NF is converted to a known form of Se following ingestion and absorption, the NF is to be treated as a xenobiotic with unknown properties in the body. From a subchronic toxicity study in rats, the Panel derives a lowest observed adverse effect level (LOAEL) for general toxicity of 2 mg Se/kg body weight (bw) per day based on findings indicating liver as a target organ, as it has been shown for other studies on dietary Se. The Panel concludes that the NF is absorbed and provides Se, but in an unknown form of which the bioavailability has not been determined. The Panel also concludes that the safety of the NF under the intended conditions of use cannot be established.

Keywords: novel food, nutrient source, selenite triglycerides, selenium, food supplement, safety, bioavailability

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1. Introduction

The present opinion deals with the assessment of a mixture of several selenite triglycerides obtained from selenisation of triglycerides in sunflower oil. Selenite triglycerides are proposed as a novel food and as a source of selenium.

1.1. Background as provided by the European Commission

The dossier relating to selenite triglycerides as a source of selenium was submitted to Chief Sanitary Inspectorate, the competent authority for novel food in Poland, for an initial assessment under Article 6(2) of Regulation (EC) No 258/97 concerning novel foods and novel food ingredients.

The European Union legislation lists nutritional substances that may be used for nutritional purposes in certain categories of foods as sources of certain nutrients.

The relevant Union legislative measures in force at that time were:

- Regulation (EC) No 258/97 of the European Parliament and the Council concerning novel foods and novel food ingredients.[1]
- Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements.[2]

On 14 March 2011, Chief Sanitary Inspectorate of Poland forwarded to the Commission the initial assessment report, concluding that the novel food ingredient meets the requirements of Article 1(3) of Regulation (EC) No 258/97 on recommended doses.

On 25 March 2011, the Commission forwarded the initial assessment report to the other Member States (MS). Several MS raised objections or submitted comments.

The concerns of a scientific nature raised by the MS can be summarised as follows:

- lack of characterization of the product
- potential presence of uncharacterized impurities and by-products and their impact on the safety of the product
- target groups, proposed uses, expected intake not clearly defined
- no information about the chemical compounds measured in the pharmacodynamic studies
- lack of experimental data on the biological activity of the absorbed compounds
- lack of scientific data on chronic toxicity and human exposure.

On 30 April 2015 and in accordance with Article 29(1)(a) of Regulation (EU) 178/2002[3], the Commission asked the European Food Safety Authority to provide a scientific opinion by carrying out the additional assessment for selenite triglycerides as a NF in the context of Regulation (EU) No 258/97 to consider the elements of a scientific nature in the comments raised by the other MS.

According to Article 35 (1) of Regulation (EU) 2015/2283[4], any request for placing a novel food on the market within the Union submitted to a Member State in accordance with Article 4 of Regulation (EU) 258/97 and for which the final decision has not been taken before 1 January 2018 shall be treated as an application under Regulation (EU) 2015/2283. This is the case for this application.

In accordance with Article 10 (3) of Regulation (EU) 2015/2283, EFSA shall give its opinion as to whether the update of the Union List referred to in Article 10 (1) is liable to have an effect on human health.

In addition, as the requested use of the novel food ingredient is as a source of selenium in food supplements, in order to include selenite triglycerides in Annex II to Directive 2002/46/EC on food supplements as a source of selenium, the Commission asks EFSA to provide advice both on the safety and bioavailability of the above mentioned substance.

[1] Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients.

[2] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements OJ L 183, 12.7.2002, p. 51–57.

[3] Regulation (EU) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

[4] Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001 (2013/0435 (COD). OJ L 327, 11.12.2015, p. 1–22.

1.2. Terms of Reference as provided by the European Commission

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002[5], the European Commission asks the European Food Safety Authority to provide a scientific opinion:

- by carrying out the additional assessment for selenite triglycerides as a novel food ingredient in the context of Regulation (EC) No 258/97, and
- following the outcome of the novel food assessment by evaluating the safety of selenite triglycerides, when added for nutritional purposes to food supplements as a source of selenium and on the bioavailability of selenium from this source, in the context of Directive 2002/46/EC.

1.3. Information on existing evaluations and authorisations

Selenium

Selenium (Se) rarely occurs in nature in its elemental state, whereas it forms several water-soluble inorganic and organic compounds. Inorganic species include selenide ions (Se^{2-}); selenite ions (SeO_3^{2-}), where selenium is present as Se(IV); selenate ion (SeO_4^{2-}), where selenium is present as Se(VI). Selenate is the most common inorganic form of Se found in water (Vinceti et al., 2013); in some foods (e.g., seafood, legumes and dry fruit) inorganic Se (in the form of selenate and selenite) appears as major species in addition to the organic ones, while the organic species are predominant in other foods such as beef and poultry (Fairweather-Tait et al., 2011; Filippini et al., 2018). Se is generally found in trace amounts in the above-mentioned matrices ($\leq$ 1 mg/kg), with the exception of Brazilian nut (20 mg/kg). Selenium forms stable bonds with carbon in organic selenium compounds. Organoselenium compounds include selenides (R–Se–R), naturally occurring selenium amino acids (L-selenomethionine or L-selenocysteine in which selenium is incorporated as a substitute of sulfur) and selenoproteins; the latter include iodothyronine deiodinase, glutathione peroxidases, thioredoxin reductases and selenoprotein P. Selenium, as L-selenocysteine, is essential to humans for the synthesis of selenoproteins (EFSA NDA Panel, 2014).

The Scientific Committee on Food (SCF, 2000) adopted a tolerable upper intake level (UL) of 300 μg/day for adults including pregnant and lactating women, on the basis of a no observed adverse effect level (NOAEL) of 850 μg/day for clinical selenosis and applying an uncertainty factor of 3, supported by three studies reporting no adverse effects for selenium intake between about 200 and 500 μg/day for duration ranging from 6 weeks to 10 years. As there were no data to support a derivation of a UL for children, the SCF (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). It is acknowledged that inorganic Se forms are reported to be generally more toxic than organic Se forms, but this factor is not considered in the current UL (Fairweather-Tait et al., 2011).

In 2014, the EFSA NDA Panel issued a scientific opinion on the dietary reference values (DRVs) for selenium (EFSA NDA Panel, 2014). The levelling off of plasma selenoprotein P (SEPP1) concentration was considered indicative of an adequate supply of selenium to all tissues and to reflect saturation of the functional selenium body pool, ensuring that selenium requirement is met. However, evidence from human studies on the relationship between selenium intake and plasma SEPP1 was insufficient to derive an average requirement and the Panel set an adequate intake (AI) of 70 μg/day for adults and 15 μg/day for infants aged 7–11 months, with intermediate values in the range 15 μg/day for children aged 1–3 years up to 70 μg/day for adolescents aged 15–17 years. For lactating women, an AI of 85 μg/day was set to cover the amount of selenium secreted in breast milk.

Several substances are currently authorised as sources of selenium for addition to foods[6] and some categories of food for special groups[7] (selenium-enriched yeast, sodium selenite, sodium hydrogen selenite, sodium selenate) and for use in the manufacture of food supplements[8]

[5] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety OJ L 31, 1.2.2002, p. 1–24.

[6] 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.

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

[8] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements.

(L-selenomethionine, selenium-enriched yeast, selenous acid, sodium selenite, sodium hydrogen selenite, sodium selenate).

The NDA Panel has also evaluated 10 health claims related to selenium pursuant to Article 13(1) of Regulation (EC) No 1924/20065.[9] The safety assessment was not considered in the framework of health claim evaluation.

2. Data and methodologies

2.1. Data

The safety assessment of this NF is based on data supplied in the application and information submitted by the applicant following EFSA requests for supplementary information.

Administrative and scientific requirements for NF applications referred to in Article 10 of Regulation (EU) 2015/2283 are listed in the Commission Implementing Regulation (EU) 2017/2469.

A common and structured format on the presentation of NF applications is described in the EFSA guidance on the preparation and presentation of a NF application (EFSA NDA Panel, 2016). As indicated in this guidance, it is the duty of the applicant to provide all of the available (proprietary, confidential and published) scientific data, including both data in favour and not in favour to supporting the safety of the proposed NF.

This NF application does not include a request for the protection of proprietary data.

2.2. Methodologies

The assessment was conducted in line with the principles described in the EFSA Guidance on transparency in the scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing Guidance documents from the EFSA Scientific Committee.

The NDA Panel assessed the safety of selenite triglycerides in line with the principles contained in the latest existing guidance on the safety evaluation of novel foods, namely the Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283 (EFSA NDA Panel, 2016).

The evaluation of bioavailability of the nutrient (selenium) from the source (selenite triglycerides) was conducted in line with the principles contained in the Guidance on safety evaluation of sources of nutrients and bioavailability of nutrient from the sources (EFSA ANS Panel, 2018).

3. Assessment

3.1. Introduction

The proposed novel food (NF) is a synthetic product obtained by the reaction between oxidised sunflower oil and selenous acid and consists of a mixture of selenite triglycerides. It falls under category i) of the novel food regulation,[10] i.e. food with a new or intentionally modified molecular structure, where that structure was not used as, or in, a food within the Union before 15 May 1997. The NF is proposed to be used as an ingredient in food supplements. The target population is children above 12 years of age and adults.

3.2. Identity of the novel food

The NF, intended to be commercialised as Selol® 5%, is a red-orange oil, transparent, with a characteristic faint smell. It is composed of a mixture of Se-containing triglyceride derivatives obtained from the reaction of triglycerides from sunflower oil with selenous acid. The NF proposed to be placed on the market contains approximately 5% m/v of selenium (50 mg Se/mL).

The NF is composed of a mixture of several Se-containing triglyceride derivatives, depending on the fatty acids profile of the initial sunflower oil. The proposed mechanism of the triglyceride selenisation excludes the possibility of selenium incorporation into saturated fatty acid residues of triglycerides.

[9] EU Register on nutrition and health claims, accessible at https://ec.europa.eu/food/safety/labelling_nutrition/claims/register/public/

[10] Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001.

Linoleic and oleic acids are the predominant fatty acids in sunflower oil triglycerides (constituting up to 90%) and are the two major unsaturated fatty acids being selenised during the production process. An example of the structure of a possible selenite triglyceride present in the final product is provided in Figure 1.

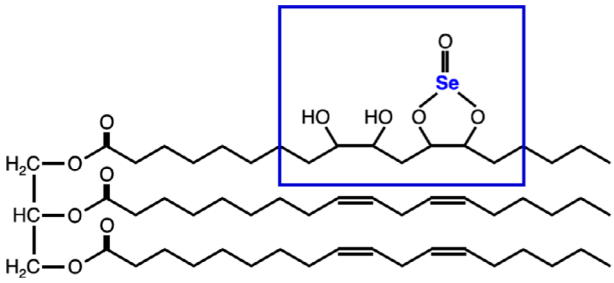

Figure 1: Example of one of the possible selenite triglycerides present in the NF (from Sonet et al., 2019)

3.3. Production process

The production process, performed at laboratory scale and claimed confidential by the applicant, can be summarised as follows. In the first stage, sunflower oil triglycerides react with $KMnO_4$ under controlled temperature and hydroxylation of some double bonds of unsaturated fatty acids occurs. The product obtained is mixed with selenous acid dissolved in dioxane, with the use of amorphous selenium as a catalyst. The resulting mixture is purified via vacuum distillation and the fraction of selenised triglycerides containing 5% of selenium is separated by high-performance liquid chromatography (HPLC).

According to the applicant, under the process conditions employed only a small number of double bonds of unsaturated fatty acids undergoes hydroxylation and subsequent selenisation with selenous acid forming dioxaselenolane rings.

The Panel notes that the starting material used, i.e. sunflower oil, is a commercial product, the composition of which is not under the control of the applicant. The Panel considers that the production process is sufficiently described and does not raise safety concerns.

3.4. Compositional data

According to the applicant, the product obtained at the end of the synthesis contains more than 40 different compounds of similar structure, and the fractionation step separates the fraction containing 5% Se, corresponding to the NF.

The applicant provided mass spectrometry (MS) analyses of the NF (HPLC–ICP-MS and HPLC-Electrospray-Orbitrap Tandem MS) (Bierla et al., 2016). A total of 11 selenium-containing triglyceride derivatives resulting from the oxidation of one or two double bonds of linoleic acid and analogous derivatives of glycerol linoleate(s)/oleinate(s) were identified. They accounted for approximately 60% of total selenium in the product. The authors indicated that an additional 35% of total selenium was likely to be present in the form of mixed unsaturated/saturated triglyceride derivatives.

Upon request of the Panel (see Steps taken by EFSA, number 7), the applicant provided the results of analyses aiming at further characterising the NF. These additional analyses were carried out by means of HPLC-UV (230 nm), ^{13}C and ^{1}H NMR and electrospray ionisation (ESI) mass spectrometry. However, the obtained results do not allow the unequivocal identification of the components of the mixture, due to the complexity of the mixture. The HPLC-UV analysis identified a characteristic chromatographic profile for the distribution of Se in the NF with 24 different peaks containing Se that was used by the applicant as standard for the identification of the NF in the batch-to-batch analysis. However, it is noted that the identification of the selenium-containing chemical species present in the samples analysed was not provided.

Upon request of the Panel (see Steps taken by EFSA, number 7), the applicant also discussed the fate of the non-triglyceride fraction of sunflower oil after the production process. In particular, the applicant provided a rationale without providing data, for the possible reactions of lecithin, tocopherols, carotenoids, waxes, free fatty acids and polyphenols occurring during the synthesis

according to which such reactions – with the only exception of free fatty acids – occur to a negligible extent.

In order to confirm that the production process is reproducible, the applicant provided the results of five subsequent production batches of the NF obtained in independent laboratory syntheses performed at weekly intervals starting from the same batch of sunflower oil (Table 1). Upon request of the Panel (see Steps taken by EFSA, number 7), the applicant provided analyses of three batches (one of which already provided) for peroxide value, anisidine value, concentrations of arsenic, cadmium and lead, complementing the batch-to-batch analyses already submitted.

To confirm the reproducibility of the synthesis the applicant also provided the HPLC-UV chromatograms (λ = 230 nm) of five of the batches of the NF reported in Table 1. The overlay of the chromatograms indicated similar peak profiles, retention times and intensities of the five samples. The results indicate that the synthesis of selenite triglycerides from the same batch of sunflower oil yields reproducible products.

The Panel notes that the most comprehensive study provided (Bierla et al., 2016) was able to characterise only 60% of the NF, while making reasoned assumptions for the remaining fraction. The additional analyses submitted did not provide a full identification of the compounds contributing to the distribution of Se in the chromatographic profile. The Panel also notes that the batch-to-batch analyses were performed on samples produced from the same batch of sunflower oil. The Panel finally notes that the applicant, asked for analyses of the heavy metals in the NF, did not provide analyses for mercury.

The Panel considers that the information provided does not allow a complete characterisation of the composition of the NF and is therefore considered insufficient.

Table 1: Batch-to-batch analysis of the novel food

Parameter	Method of analysis	Batch # 051115	Batch # 101215	Batch # 121115	Batch # 191115	Batch # 261115	Batch # 091117[a]	Batch # 081118[b]
Form and properties	Visual inspection	Conform	Conform	Conform	Conform	Conform	–[c]	–
Identification[d]	HPLC	Conform	Conform	Conform	Conform	Conform	–	–
Relative density	Ph. Eur. 2.2.5	0.991	0.989	0.991	0.991	0.990	–	–
Acid value (*IA*)	Ph. Eur. 2.5.1	0.38	0.09	0.31	0.36	0.36	–	–
Peroxide value	ISO 3960	–	–	–	–	5.91 ± 0.68	4.03 ± 0.37	1.92 ± 0.22
p-Anisidine value	ISO 6885	–	–	–	–	64.88± 1 0.10	72.88 ± 11.70	57.64 ± 12.49
Unsaponifiable matter, %	Ph. Eur. 2.5.7	0.60	0.38	0.66	0.65	0.28	–	–
Total content of selenium, mg/g	ICP-MS	53.0	50.8	52.2	52.0	52.0	–	–
Selenous acid, μg/g	ICP-MS	0.004	0.010	0.015	0.009	0.018	–	–
Dioxane, μg/g	Ph. Eur. 2.4.24	5.60	6.39	6.61	6.54	5.99	–	–
Amorphous selenium (↓Se0), mg/g	ICP-MS	0.008	0.08	0.003	0.002	0.009	–	–
MnO_2, μg/g	ICP-MS	1.5	1.2	1.4	1.3	1.2	–	–
Arsenic, μg/g	ICP-MS	–	–	–	–	0.23	0.25	0.25
Lead, μg/g	ICP-MS	–	–	–	–	0.002	0.004	0.005
Cadmium, μg/g	ICP-MS	–	–	–	–	0.36	0.11	0.04
Total aerobic microbial count	Ph. Eur. 2.6.12	< 10 CFU/mL	< 10 CFU/mL	< 10 CFU/mL	< 10 CFU/mL	< 10 CFU/mL	–	–
Total yeast and moulds count	Ph. Eur. 2.6.12	< 10 CFU/mL	< 10 CFU/mL	< 10 CFU/mL	< 10 CFU/mL	< 10 CFU/mL	–	–
Escherichia coli	Ph. Eur. 2.6.13	Absent in 1 mL	Absent in 1 mL	Absent in 1 mL	Absent in 1 mL	Absent in 1 mL	–	–

HPLC: high-performance liquid chromatography; Ph. Eur: European Pharmacopeia; ICP-MS: inductively coupled plasma mass spectrometry; CFU: colony forming unit.
(a): Analysed 1 year after the synthesis.
(b): Analysed 3 years after the synthesis.
(c): – = not analysed.
(d): Composition of selenite triglycerides. It is noted that the analytical method is unable to provide identification of the selenium-containing chemical species present in the sample.

3.4.1. Stability

The applicant provided the result of the stability studies of three batches of the NF conducted for 12 months in sealed glass amber bottles under controlled intermediate conditions (30 ± 2°C/60% relative humidity (RH) ± 5%). The results of all the parameters analysed in the tests (i.e. composition of selenite triglycerides, relative density, acid value, unsaponifiable matter, total content of selenium, contamination with selenous acid, contamination with amorphous selenium) were all within those set in the specifications.

Upon request of the Panel to assess the oxidative stability of the product by means of its peroxide value and its anisidine value (see Steps taken by EFSA, number 7), the applicant provided the results of three batches produced at different times and analysed at one single time point (shortly after synthesis, after one year and after 3 years from the synthesis). These results are reported together with the batch-to-batch analyses (Table 1). The results indicate that both the peroxide and the *p*-anisidine values were within the specifications proposed; it is nevertheless noted that, to account for methodological limitations with the official method for *p*-anisidine value due to lipid nature of the product, the applicant set a specification limit which is considered by the Panel as being too high (see Section 3.5).

The Panel considers that the data provided sufficient information with respect to the stability of the NF for 12 months.

3.5. Specifications

The specifications for selenite triglycerides as proposed by the applicant are reported in Table 2.

Table 2: Specifications for selenite triglycerides as proposed by the applicant

Description	The NF is a red-orange oil, transparent, with a characteristic faint smell. It is composed of a mixture of selenite triglycerides obtained from the esterification of hydroxylated triglycerides from sunflower oil with selenous acid. The NF contains approximately 50 mg Se/mL	
Parameter	**Specification value**	**Method of analysis**
Form and properties	Clear, red-orange oil, weak characteristic smell	Visual inspection
Solubility	Substance is soluble in benzene, hexane, ethyl ether, dichloromethane and dioxane	Visual inspection
Identification	1. After the reaction of substance (oil) with trifluoroacetic acid in dichloromethane the mixture has an intense red colour (Suchocki et al., 2003)	1. Visual inspection
	Alternative methods through comparison with spectra and analyses similar to reference ones from:	
	1. ^{1}H and ^{13}C NMR spectra in $CDCl_3$ 2. Elemental analysis and HPLC-ESI-MS chromatograms and mass spectra	1. NMR 2. HPLC-ICP-MS HPLC-ESI-MS
Relative density	0.975–1.000	Ph. Eur. 2.2.5
Acid value (IA)	≤ 0.5, determined on 10.0 g	Ph. Eur. 2.5.1
Peroxide value	≤ 10 meq/kg	Ph. Eur. 2.5.5
p-Anisidine value	≤ 80	Ph. Eur. 2.5.36
Unsaponifiable matter	≤ 1.5%, determined on 5.0 g	Ph. Eur. 2.5.7
Total content of selenium	45.0–55.0 mg in 1 g	ICP-MS
Selenous acid (H_2SeO_3)	≤ 0.1%	ICP-MS
Dioxane	≤ 20 μg/g	Ph. Eur. 2.4.25
Amorphous selenium (↓Se0)	≤ 0.5%	ICP-MS
MnO_2	≤ 20 μg/g	ICP-MS
Arsenic	≤ 0.3 mg/kg	ICP-MS

NMR: nuclear magnetic resonance; ESI-MS: electrospray ionisation mass spectrometry; HPLC: high-performance liquid chromatography; ICP-MS: inductively coupled plasma mass spectrometry; Ph. Eur: European Pharmacopeia.

The Panel considers that given the nature of the NF and the compositional analyses discussed in Section 3.4, none of the analytical methods proposed was able to achieve a complete identification of the NF. The Panel also notes that the specification limit proposed for p-anisidine value is considered

too high (Matthäus, 2010). The Panel considers that the remaining information provided on the specification of the NF is sufficient and does not raise safety concerns.

3.6. History of use of the NF and/or of its source

The NF is produced from commercially available sunflower oil. No data are available on the human consumption of the NF.

The Panel notes that selenite triglycerides are non-naturally occurring lipophilic selenium compounds. There are no other known sources of these compounds in the human diet.

3.7. Proposed uses and use levels and anticipated intake

3.7.1. Target population

The NF is intended to be used in food supplements for children above 12 years of age and adults.

3.7.2. Proposed uses and use levels

The applicant requests the inclusion of selenite triglycerides as a source of selenium in food supplements among the authorised substances included in Annex II of Directive 2002/46/EC.

The NF is intended to be used in food supplement at levels that would provide an intake up to 1 and 2 mg/day of the NF in children above 12 years of age and adults, respectively. This corresponds to an intake of up to 50 μg Se/day in children above 12 years of age and up to 100 μg Se/day in adults.

3.8. Absorption, distribution, metabolism and excretion (ADME)

3.8.1. Fate in model gastric fluid

The applicant was requested to provide data from a dissociation test and an appropriately designed *in vitro* study aiming at assessing the fate of the NF under gastrointestinal conditions, to demonstrate in which chemical form selenium is released from the source and becomes available for absorption in the gastrointestinal tract. (see Steps taken by EFSA, number 9). The data requested were not provided.

3.8.2. Absorption and distribution

Selol 2% (a product similar to the NF, containing 20 instead of 50 mg Se/mL) diluted with vegetable oil was administered to male Wistar rats via oral or subcutaneous route at the dose of 12 mg Se/kg body weight (bw) (Jastrzębski et al., 1997). The content of Se was determined in blood and tissues (brain, cerebellum, lungs, heart, liver, kidneys, spleen, testis and adrenal glands) at different time points from 0.5 to 6 h and pharmacokinetic analyses were performed. According to the authors, following oral administration, an increase of total selenium was observed in blood and all tissues. The selenium blood concentration reached the highest level of 494 ± 8 ng/mL at 1.9 ± 0.1 h and an area under the selenium concentration time curve ($AUC_{0\rightarrow\infty}$) of 1,373 ± 56 ng/h per mL was calculated. However, selenium concentration was monitored only from 0.5 to 6 h after oral administration. The Panel notes that the quantification method employed does not allow to determine the form of Se analysed. Furthermore, the lack of a control group and information on the baseline levels (t = 0) of Se in the tissues analysed does not allow to draw reliable conclusions on the findings reported.

Upon request of the Panel (see Steps taken by EFSA, number 9), the applicant provided results extracted from a pharmacokinetic study where male Wistar rats (15–17 weeks of age, weight between 250 and 350 g) were tested with the NF or sodium selenite (no study report available). Three animals per group received via intragastrical administration either the NF diluted in sunflower oil at a dose equivalent to 12 mg of Se/kg bw or sodium selenite dissolved in water at a dose equivalent to 2 mg of Se/kg bw. Multiple blood samples were taken over a period of 72 h, and at the last observation time point, the rats were sacrificed and liver and kidneys were harvested. The study indicated that upon ingestion of the NF the mean plasma Se concentration time curve had a profile similar to sodium selenite. The ($AUC_{0\rightarrow\infty}$) was 453 and 323 mg/h/L for the NF and sodium selenite, respectively, and taking into account the higher Se dose from the NF, the relative bioavailability of Se from the NF diluted in sunflower oil was approximately 24% compared to sodium selenite dissolved in water. Selenium levels in rat liver were 103.76 ± 23.78 and 95.86 ± 26.41 μg/g tissue after administration of

the NF and sodium selenite, respectively, whereas corresponding levels in kidneys were 118.98 ± 17.11 and 63.08 ± 3.77 μg/g tissue. The results of the study indicate that the NF is a source from which Se is bioavailable in an unknown form and most likely with a lower bioavailability than selenite. The Panel notes that despite the uncertainties due to the lack of information on the background levels of Se in the target tissues and the lack of characterisation of the form(s) of Se analysed, the study indicates a difference in distribution of Se to the kidneys between the NF and selenite, which may indicate the presence of different forms of Se circulating. The Panel notes that the doses administered in the study are orders of magnitude higher than the proposed anticipated intake of the NF and therefore the relevance of the study is limited.

In a publication by Sonet et al. (2019), the cellular uptake of Se from the NF was compared to that of selenite and selenate. Cancerous (LNCaP) and immortalised (HEK293 and PNT1A) cell lines were used in the study. The study indicated a similar uptake of Se in the different cell lines but a different metabolism, as observed by the incorporation of Se in selenoproteins in HEK293 and LNCaP cell lines, but not in PNT1A. The Panel considers that the study does not help in defining the bioavailability of Se from the NF as a dietary source.

3.8.3. Metabolism

Metabolites in rat blood serum and erythrocytes

The applicant provided the description and results of a study in rats aiming at assessing the fate of the NF and its metabolites in blood serum and erythrocytes following administration of the NF per os at a dose corresponding to 20 mg Se/kg bw (no study report available). Rats were divided into 14 groups of five animals each, one control group receiving sunflower oil and 13 groups where blood samples were collected from the heart at different time points up to 48 hours after administration. The fate of the NF and its metabolites was assessed in blood serum and erythrocytes.

The applicant isolated, through HPLC fractionation, metabolites of the NF from rat blood serum. Based on UV chromatograms (λ = 230 nm) of the samples collected at 0.5, 1.5, 4 and 12 h after administration of the NF, the applicant attributed peaks in two regions of the chromatogram as being selenite triglycerides bonded to thiols and selenite triglycerides bonded to thiols and proteins. According to the applicant, the area of the peaks related to selenite triglycerides bonded to thiols and proteins had a maximum in the sample at 1.5 h from dosing and decreased after 4 h, while the peaks related to selenite triglycerides bonded to thiols were still present after 12 h. The applicant concluded that bound selenite triglycerides reach the blood and undergo decomposition, i.e. chains of saturated fatty acids (palmitic or stearic acid) detach from selenite triglycerides, giving rise to selenite diglycerides that further detach from proteins. To support this conclusion the applicant reports on the characterisation through ESI-MS of the components of one of the peaks identified in the chromatogram of the sample after 12 h from dosing with Selol 10% (a product similar to the NF, containing 100 instead of 50 mg Se/mL) and proposed the possible structure of five selenite diglycerides being present in the chromatographic peak. Furthermore, the applicant observed that total selenium in rat blood serum reached a maximum in the sample taken 1.5 h after dosing.

In the same study, the applicant reported HPLC analyses of the erythrocyte component of the samples collected from rats after 0.5, 1 and 2.5 h from dosing. Similar chromatographic profiles to the ones obtained for serum were reported for the group of peaks attributed to selenite triglycerides bonded with thiols and for the peak attributed to the mixture of various selenite diglycerides. Dynamics similar to those observed in the chromatograms described for blood serum were observed also in the case of erythrocytes. The applicant claims that higher Se concentration are reached in these samples due to the ability of the erythrocytes to pick up Se from blood serum.

The applicant also assessed the effects on the concentration of thiols and redox state in rat brain homogenates from the same study. The concentration of glutathione in rat brain cells was found to increase four times and a temporary perturbation of the redox state was observed. The authors concluded that administration of 20 mg of Se/kg bw in the form of the NF to rats causes oxidative stress, which triggers the non-enzymatic antioxidant system.

A follow-up morphological study assessed the subcellular structure of cerebral cortex samples of rats at 0, 24 and 48 h after administration of the NF. Electron microscopy did not show changes in the animals administered the NF compared to the control.

The Panel considers that no supporting evidence is provided in the study on the actual identification and characterisation of the compounds discussed. It is therefore unclear in which form Se is present in blood and tissues. The applicant only reports on the mass spectrometric identification of one class of

potential metabolites, i.e. selenite diglycerides, in rat blood serum, without providing supporting evidence.

Other studies

The applicant described additional studies investigating the concentration of Se, the activity of selected enzymes and the redox status of blood and animal tissues following administration of the NF to healthy mice (unpublished report; Sochacka et al., 2018), and the consequences of changes in selenium concentration and redox state in cancer cell lines (Flis et al., 2015). The Panel notes that in those studies the NF induced complex and contradictory alteration of the redox status of the test systems, including the possible induction of oxidative stress and increase of malondialdehyde. The Panel considers that these studies do not add to the body of evidence on the metabolism of the NF after absorption.

3.8.4. Excretion

The applicant reports on a study performed to evaluate the presence of selenium-containing compounds following administration of the NF, in urine and in faeces in rats and humans, and in expired air in humans. Rats were administered the NF in a dose equivalent to 10 mg Se/kg bw. Volunteers were administered single doses of the NF equivalent to 40 mg Se, corresponding to 0.5 mg Se/kg bw. The material was collected starting 3 hours after the administration of the NF, and analysed via MS and ICP-MS. In the urine of both rats and humans, the applicant reports the presence of trimethylselenonium ions, small amounts of selenite diglycerides of various structures and different compounds of Se(II) (selenide) with metals such as Pb and Zn (the latter in humans only). In faeces in rats, the applicant reports the presence of different compounds containing Se and phosphorus and Se (II) along with Pb and Zn. In expired air in humans, dimethyl selenide was claimed to be observed at 6–9 h after administration of the NF. The Panel considers that the limitations in the description of the study (no study report available, type of administration not specified, length of the study not specified, analytical results not provided) preclude an adequate assessment of the evidence provided.

3.8.5. Bioavailability of selenium from selenite triglycerides

Section 3.8.2 discusses a pharmacokinetic study in which the NF was tested against sodium selenite, an authorised source of selenium according to Directive 2002/46/EC. The Panel considers that the results indicate that selenite triglycerides are a source from which Se is bioavailable in an unknown form and most likely with a lower bioavailability than selenite. However, as noted, the relevance of the study is limited when the proposed use levels are considered and the actual bioavailability of the Se form(s) provided by the NF at the proposed use levels remains not characterised.

3.9. Nutritional information

The NF is composed of triglycerides obtained from sunflower oil partially hydroxylated and selenised to contain approximately 50 mg Se per mL NF (5%) (Section 3.2).

Selenite triglycerides are non-naturally occurring lipophilic organic selenium compounds. There is insufficient evidence that they provide Se in a form than can be utilised (i.e. enter the functional Se body pool to fulfil Se physiological functions) and to what extent this may happen. Therefore, the nutritional value of the NF cannot be established.

The Panel considers that taking into account the composition of the NF and the proposed conditions of use it cannot be established whether or not the consumption of the NF is nutritionally disadvantageous.

3.10. Toxicological information

The applicant provided genotoxicity, *in vitro* toxicity, acute toxicity and subchronic toxicity studies, which are listed in Table 3.

Table 3: List of toxicological studies with the NF

Test item	Reference	Type of study	Test system	Dose
NF	National Medicines Institute (2016)	Bacterial reverse mutation test	*Salmonella* Typhimurium TA97, TA98, TA100 and TA102	Up to 5,000 μg Se/plate (absence and presence of S9 mix)
NF	Rahden-Staroń et al. (2010)	Bacterial reverse mutation test	*S.* Typhimurium TA97a, TA98, TA100, TA1535 and TA102	Up to 5% corresponding to 5,000 μg Se/plate (absence and presence of S9 mix)
NF micelles	National Medicines Institute (2018)	*In vitro* mammalian cell micronucleus test	Mouse fibroblasts NCTC clone 929, ATCC	2 mg/mL (absence and presence of S9 mix)
Selol (unknown % selenium)	Jastrzębski et al. (1995)	Acute toxicity study	Male Wistar rats	Up to 200 mg/kg bw oral gavage Up to 100 mg/kg bw intraperitoneal Up to 500 mg/kg bw subcutaneous
		Cumulative toxicity study	Male Wistar rats	Up to 154 mg/kg bw oral gavage
NF	Institute of Industrial Organic Chemistry (2017)	90-day repeated dose oral toxicity study	Wistar rats	Up to 32 mg/kg bw per day

bw: body weight; GLP: good laboratory practice; OECD TG: Organisation for Economic Co-operation and Development – Test guideline.

3.10.1. Genotoxicity

In a bacterial reverse mutation test (Ames test), the NF was tested on four *Salmonella* Typhimurium tester strains, i.e. TA97, TA98, TA100 and TA102 (National Medicines Institute, 2016; PN-EN ISO 10993-3:2014 and 10993-12-2012; unpublished). The NF did not induce a biologically relevant increase in the number of revertant colonies compared to the negative controls (dimethyl sulfoxide (DMSO) and sunflower oil), in any of the strains when tested up to a declared content of selenium(IV) of 5,000 μg/plate in the presence or absence of a metabolic activation system (S9). The NF was thus not mutagenic in this assay. The Panel notes that information on GLP compliance is lacking and the study design and the study did not comply with OECD Test Guideline (TG) 471 since only four strains and three doses were used.

The applicant provided reference to a publication on a second Ames test in which the NF was tested on five *S.* Typhimurium tester strains, i.e. TA97a, TA98, TA100, TA1535 and TA102 (Rahden-Staroń et al., 2010). Information on GLP compliance was not provided. Using the plate incorporation method (in the presence and absence of S9) and the pre-incubation method (only in the presence of S9), the NF did not induce an increase in the number of revertant colonies in any of the strains compared with the negative controls (DMSO and acetone:water = 1:1) when tested at doses of selenium of 330, 500, 1,000 and 5,000 μg/plate, respectively. The NF was thus not mutagenic in this assay.

Upon request of the Panel (see Steps taken by EFSA, number 3), the applicant provided an *in vitro* micronucleus test (National Medicines Institute, 2018; PN-EN ISO 10993-3:2014 and 10993-12-2012; unpublished) where the NF was tested in the form of micelles because the physical form of the NF (oil) did not allow conducting the test according to OECD TG 487 recommendations. The NF did not increase the number of micronuclei compared to control when tested at concentration of 2 mg/mL, either in the presence or absence of a metabolic activation system. The authors indicated that the NF is non-genotoxic at concentration of 2 mg/mL. The Panel notes that no reliable conclusions can be drawn from this micronucleus test due to the limitations in the study design, the use of only one dose level, the lack of information on cytotoxicity and limited data reporting.

The Panel therefore concludes that the information provided is insufficient to characterise the potential genotoxicity of the NF.

3.10.2. Other toxicity studies

A publication by Jastrzębski et al. (1995) reported the results of an acute and cumulative toxicity study performed on male Wistar rats where groups of 10 animals were tested with SeIol (% Se not reported). In the acute toxicity study, the intake by oral gavage resulted in an acute higher toxicity (A-LD_{50} = 100 mg/kg bw) compared to groups where the NF was administered intraperitoneally or subcutaneously (doses tested were up to 200, up to 100 and up to 500 mg/kg bw respectively). In the cumulative toxicity study, rats were tested by oral gavage up to 154 mg/kg bw. A mean lethal dose C-LD_{50} of 85 mg/kg bw was found. The Panel considers that acute toxicity studies are not relevant for safety assessment of NFs.

3.10.3. Subchronic toxicity

Upon request of the Panel (see Steps taken by EFSA, number 3), the applicant performed a modified 90-day repeated dose toxicity study (Institute of Industrial Organic Chemistry, 2017; OECD TG 408 with extended parameters from OECD TG 407; unpublished). The NF was administered daily by gavage to four groups of Wistar rats (10/sex) at doses of 0 (control), 2 (low dose), 8 (mid dose) or 32 mg Se/kg bw (high dose); two additional recovery groups (10/sex) received either the control or the highest dose tested.

All animals survived the experiment. Clinical signs were observed in five animals of both sexes in all dose groups, and included thinning of hair coat, alopecia, respiratory murmurs and salivation. The Panel notes that hair loss and changes in skin are typically observed in selenosis (Chawla et al., 2020). Ophthalmic examinations did not reveal any pathomorphological changes. Body weights were not statistically significantly different for treated and control groups and food intake was similar in all groups.

Slight to moderate changes in arousal were observed in few animals of both sexes. No involuntary clonic and tonic movements, changes in gait, or stereotypical behaviour were observed. Pain reaction latency time was shorter in males in the high-dose group and females in the recovery groups administered the NF, and longer in females in mid- and high-dose groups, compared to the controls. A statistically significant increase of the horizontal locomotor activity was observed in the time interval 0–10 min for males in the high-dose group, and 10–20 min for females in the high-dose group.

Mean corpuscular value (MCV) was statistically significantly reduced in animals at the highest dose in both sexes. Reticulocytes and prothrombin time were found to increase and thrombocytes to decrease in females in the high-dose group. Creatinine was decreased in all female groups in a dose-dependent manner (−10%, −19% and −29% in the low-, mid- and high-dose groups, respectively), with the effect persisting in the recovery group, and in males at the highest dose (−18%). Statistically significantly increased concentrations of albumin and calcium in males tested with mid and high dose and increased albumin/globulin in males in the high-dose group were observed. Increased activity of alkaline phosphatase (AP) and glutamic pyruvic transferase (ALT) were observed in females at the highest dose. The recovery groups tested with the NF indicated reversibility of some observed changes (thrombocytes and prothrombin time in females; calcium, albumin/globulin ratio in males), appearance of new ones (haemoglobin, erythrocytes, mean corpuscular haemoglobin (MCH) in males; total protein in males and females; haematocrit, MCH, albumin, cholesterol, bile acids in females) or consolidation of previous changes (creatinine in females; albumin in males; MCV in males and females; AP and ALT in females).

In both males and females tested at the highest dose increased absolute weight was observed for liver (23% in males and females, dose-related) and kidney (12% increase in males, 15% in females, dose-related), with the increase in liver being also statistically significantly different in their respective recovery groups. Increase in the absolute weight of heart and spleen and decrease of thymus and ovaries were also observed in females in the recovery group tested with the NF. Increased relative weight was observed for liver and kidney in both males and females tested at the highest dose, with liver being also statistically significantly higher in their respective recovery groups. Increase in the absolute weight of brain, heart, kidney, spleen adrenal glands was also observed in females in the recovery group tested with the NF.

The gross and histopathological examination of the liver of males and females in the high-dose group evidenced the presence of mosaic with uneven surface and granular consistency, microvesicular fatty changes of hepatocytes, individual cell necrosis of occasional hepatocytes and foci of hepatocyte degeneration, with females exhibiting an increased susceptibility to the test item. In the recovery group, the authors report a decrease in the degree of severity of liver lesions in both males and females. An increase in heart weight in females in the high-dose groups was also observed, together

with cases of heart congestion and enlargement in both males and females, which were most pronounced in high-dose groups.

The evaluation of the effect of the NF on the immune system was based on results of blood morphology through a picture of peripheral blood and bone marrow, concentration of albumin as an acute phase protein, urea, cholesterol, creatinine, total bilirubin, aspartate aminotransferase (AST), ALT, AP, total protein, albumin/globulin ratio, histopathological examination of thymus, spleen and lymph nodes as well as absolute and relative weights of thymus and spleen. Clinical chemical parameters were not affected by the NF, while on the basis of post-mortem examinations the NF at the highest dose was found to affect the weight of the spleen.

The Panel concludes that the NF at the tested doses displays a toxicological profile at least partly similar to that of dietary Se (SCF, 2000, Chawla et al., 2020) with liver as target organ (increased absolute and relative liver weight; gross and histopathological changes; decrease of creatinine and increase of ALT, AP). Effects were observed predominantly at highest doses tested and females were more susceptible to the NF. The findings seem to indicate a pattern of liver toxicity, which is dose dependent and with effects persisting in the recovery group. No relevant immunological effects were observed apart from increased spleen weight in female in the high dose group. Based on the above results, considering the decrease in creatinine level as a hallmark for liver toxicity, the lowest observed adverse effect level (LOAEL) for general toxicity in the present study was considered to be 2 mg Se/kg bw per day.

3.10.4. Chronic toxicity, carcinogenicity, reproductive and developmental toxicity

In the ADME section of the dossier submitted to EFSA, the applicant discussed the fate of the NF after ingestion. The applicant refers to data, not available to the Panel, indicating that, following administration of the NF, selenite diglycerides were identified in the serum of rats (see Section 3.8.3) and in further study, in the urine of rats and humans (see Section 3.8.4). In line with the applicable guidance document (EFSA NDA Panel, 2016; EFSA ANS Panel 2018), the Panel indicated to the applicant that if there is any evidence of absorption of selenite triglycerides as such, or other Se-lipids resulting from the production process, the applicant would be requested to perform (i) a chronic toxicity and carcinogenicity study, paying particular attention to the analysis of fatty tissues to assess potential accumulation of Se-lipid compounds; and (ii) a reproductive and developmental toxicity testing comprising a prenatal developmental toxicity study and an extended one-generation reproduction toxicity study (see Steps taken by EFSA, number 3, 5 and 9). The information requested was not provided.

3.11. Allergenicity

The Panel considers that, owing to the nature of the starting materials and process conditions, the amount of protein, if any, is expected to be very low, thus the NF is unlikely to trigger allergic reactions in the target population under the proposed conditions of use.

4. Discussion

The proposed NF is a lipophilic organic form of selenium composed by a mixture of individual Se-containing lipids. The product resulting from the production process does not occur in nature and it is the first lipophilic organic form of selenium so far described in the literature.

The Panel notes that despite the inherent natural variability of the starting material, i.e. commercial sunflower oil, the production process is sufficiently described and does not raise safety concerns.

The Panel considers that the information provided on the composition of the NF does not allow a complete characterisation of the product.

The Panel notes that no evidence was provided to demonstrate in which chemical form selenium is systemically available. The single study available for absorption and distribution, indicating that the NF provides Se in an unknown form with a possibly lower bioavailability compared to sodium selenite, does present inherent limitations and the actual bioavailability of the Se form provided by the NF at the proposed use levels remains not characterised. Despite the deficiencies in the design and reporting of the study, the Panel also notes that there seems to be a difference in distribution of Se to the kidneys when compared to sodium selenite.

The Panel notes that the applicant discusses the fate of selenite triglycerides mostly through chromatographic analyses without supporting evidence on the actual identification and characterisation of the compounds discussed. It is noted that the majority of the studies provided deals with the detection of total Se but it is unclear in which form(s) this is present. Overall, there is no convincing evidence that the NF provides Se in a form than can be utilised by the body (i.e. enters the functional Se body pool to fulfil Se physiological functions) and to what extent this may happen. Therefore, the nutritional value of the NF cannot be established.

The Panel notes that the information provided to characterise the absorption, distribution, metabolism and excretion of the NF are mostly derived from studies using doses of the NF that are not representative of the potential dietary intake. Furthermore the Panel considers that the data provided do not allow firm conclusions to be drawn on the fate of the NF following ingestion, and that, since it is not demonstrated that the NF is converted to a known form of Se following ingestion and absorption, the NF is to be treated as a xenobiotic with unknown properties in the body.

The Panel considers that owing to the limitations in the design and reporting of the genotoxicity studies and the lipophilic nature of the NF, the information provided is insufficient to characterise the potential genotoxicity of the NF.

The Panel notes that the provided subchronic toxicity study in rats indicates that the NF displays a toxicological profile which includes liver as a target organ, as it has been shown for other studies on dietary Se. From the study the Panel derives a LOAEL for general toxicity of 2 mg Se/kg bw per day, the lowest dose tested.

The Panel notes that despite the request to the applicant to provide higher tier toxicity studies in line with the EFSA guidance document, no such information was provided.

5. Conclusions

The Panel concludes that the NF is absorbed and provides Se, but in an unknown form of which the bioavailability has not been determined.

The Panel concludes that the safety of the NF under the intended conditions of use cannot be established.

Steps taken by EFSA

1) On 30 April 2015 EFSA received a letter from the European Commission with the request for a scientific opinion on the safety of selenite triglycerides as a novel food ingredient and as a source of selenium in food supplements.
2) On 07 May 2015, EFSA received from the European Commission an application on selenite triglycerides, which was submitted by BioSEL Sp. z o.o. and the scientific evaluation procedure was initiated.
3) On 18 December 2015, EFSA requested the applicant to provide additional information to accompany the application and the scientific evaluation was suspended.
4) On 13 December 2017, additional information was provided by the applicant and the scientific evaluation was restarted.
5) On 06 April 2018, EFSA requested the applicant to provide additional information to accompany the application and the scientific evaluation was suspended.
6) On 01 October 2018, additional information was provided by the applicant and the scientific evaluation was restarted.
7) On 27 November 2018, EFSA requested the applicant to provide additional information to accompany the application and the scientific evaluation was suspended.
8) On 17 January 2019, additional information was provided by the applicant and the scientific evaluation was restarted.
9) On 26 March 2019, EFSA requested the applicant to provide additional information to accompany the application and the scientific evaluation was suspended.
10) On 08 January 2020, additional information was provided by the applicant and the scientific evaluation was restarted.
11) During its meeting on 05 May 2020, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of selenite triglycerides as a novel food ingredient and as a source of selenium in food supplements.

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Abbreviations

AI	adequate intake
ALT	glutamic pyruvic transferase
ANS Panel	Panel on Food Additives and Nutrient Sources added to Food
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the curve
bw	body weight
CFU	colony forming units
DMSO	dimethyl sulfoxide
DRVs	dietary reference values
ESI-MS	electrospray ionisation mass spectrometry
GLP	good laboratory practice
HPLC	high-performance liquid chromatography
ICP-MS	inductively coupled plasma mass spectrometry
ISO	International Organization for Standardization
LOAEL	lowest observed adverse effect level
MCH	mean corpuscular haemoglobin
MCV	mean corpuscular value
MS	mass spectrometry
m/v	mass volume ratio
NDA Panel	Panel on Nutrition, Novel Foods and Food Allergens
NF	novel food
NMR	nuclear magnetic resonance
NOAEL	no observed adverse effect level
Ph. Eur.	European Pharmacopeia
OECD TG	Organisation for Economic Co-operation and Development – Test guideline
RH	relative humidity
SCF	Scientific Committee on Food
Se	selenium
SEPP1	plasma selenoprotein 1
UL	tolerable upper intake level