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## Safety of orthosilicic acid-vanillin complex (OSA-VC) as a novel food ingredient to be used in food supplements as a source of silicon and bioavailability of silicon from the source

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### Abstract

The present scientific opinion deals with the safety of orthosilicic acid-vanillin complex (OSA-VC) as a novel food ingredient for use as a source of silicon (Si) in food supplements and with the bioavailability of Si from this source. OSA-VC is stable in liquid solution at low pH values. OSA from OSA-VC was available as revealed by the increase in plasma Si concentrations after oral ingestion in human volunteers. The toxicological data provided in support of the current application were not in accordance with the Tier 1 requirement of the 'Guidance for submission for food additive evaluations'; however, this was considered justified by the Panel given that OSA-VC at pH 6.8 dissociates into orthosilicic acid and vanillin. The daily consumption of OSA-VC at the dose recommended by the applicant would provide a supplemental intake of Si of approximately 10–18 mg Si/day which would result in an estimated total intake of roughly 30–70 mg Si/day. The maximum vanillin intake resulting from the consumption of OSA-VC would be less than 5% of the acceptable daily intake (ADI) value for vanillin of 10 mg/kg body weight (bw) per day established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2002. The Panel concluded that there would be no safety concern with the proposed use and use level of OSA-VC as a novel food ingredient intended to be used as a source of Si in food supplements for the adult population. The Panel concluded that OSA, measured as Si, is bioavailable following ingestion of OSA-VC and appears similar to values reported in the literature for other established sources of OSA.

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## Summary

Following a request from the European Commission to the European Food Safety Authority (EFSA), the Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to provide a scientific opinion on the assessment of orthosilicic acid-vanillin complex (OSA-VC) as a novel food ingredient in the context of Regulation (EC) No 258/97. Following the outcome of the novel food ingredient assessment, the Panel was also asked to evaluate the safety of OSA-VC when added for nutritional purposes to food supplements as a source of silicon, and on the bioavailability of silicon from this source in the context of Directive 2002/46/EC. The safety of silicon, in terms of the amounts that may be consumed, is outside the remit of the ANS Panel.

Data from literature have established that silicon is typically present in food in the form of OSA and as such is readily absorbed from the gastrointestinal tract in humans and then readily excreted in urine. Therefore, in order to address the Terms of Reference of the current mandate, and consistently with previous scientific opinions issued on other sources of silicon, the Panel considered that bioavailability of OSA from OSA-VC as the basis for the evaluation of the bioavailability of silicon from that source.

The present assessment is based on the initial dossier submitted by the applicant and on additional data generated upon request from the Panel. The ANS Panel assessed the safety of OSA-VC as a novel food ingredient in line with the principles laid down in Commission Recommendation 97/618/EC. Limited biological and toxicological data obtained with OSA-VC were submitted by the applicant as part of the dossier. The applicant provided a justification for not complying with the Tier 1 requirements of the 2012 ANS Panel 'Guidance for submission for food additive evaluations' by demonstrating that under the conditions of simulated intestinal digestion (pH 6.8) and in the absence of digestive enzymes, the complex between OSA and vanillin is dissociated. The Panel was therefore of the opinion that no additional toxicological data were required and based its conclusions on the information available for its two components, OSA and vanillin.

The applicant has provided evidence that the two components of the complex are linked by electrostatic bonds and that the complex is stable only in an acidic environment. The Panel considered that the analytical data provided by the applicant do not fully support the identity of the material as a complex between OSA and vanillin.

With respect to the results from the stability tests of OSA-VC, the Panel noted that single measurements of pH, Si and vanillin made at the different time points did not show significant variations from the proposed specifications. The Panel considered that there would be no safety implications if the complex disassociated over time but that this could decrease the bioavailability of silicon from the proposed source OSA-VC.

With respect to the bioavailability of silicon from OSA-VC, the Panel acknowledged that this has been demonstrated only in a single randomised, placebo-controlled, crossover study conducted in 14 healthy subjects administered either 15 mL of OSA-VC solution or placebo. Plasma silicon levels were used as a surrogate for absorption and measured at baseline and at different intervals within a period of 6 hours. Urinary silicon excretion was also measured as a secondary endpoint, at baseline and after 3 and 6 hours from ingestion of either the supplement or placebo.

The study demonstrated a significant increase in the plasma silicon concentration, with maximum concentrations achieved within 3 hours from intake of supplemental silicon. Urinary excretion in the 6-hour period accounted for 21.1% of the ingested silicon dose and also in this case, it was significantly different from the placebo group.

The Panel considered the study demonstrated that OSA, measured as silicon (form of silicon not determined), is bioavailable following ingestion of OSA-VC and appears similar to values reported for other OSA sources measured as silicon in the literature.

The applicant proposed the use of OSA-VC supplement solution in a standard dose of 15 mL/day of dietary supplement (containing 98.9% OSA-VC complex), equivalent to 14.8 mL OSA-VC. The proposed use is limited to the adult population and not intended for children.

The daily consumption of OSA-VC at the daily dose recommended by the applicant would provide a supplemental intake of silicon of approximately 10–18 mg/day which would result in an estimated total intake from supplement use and from the diet of roughly 30–70 mg silicon/day, thus not exceeding the safe upper level of supplemental silicon intake of 700 mg/day of Si for adults as set by the UK Expert group on Vitamins and Minerals (EVM) in 2003.

The maximum vanillin intake resulting from the consumption of OSA-VC would be less than 0.3 mg/kg body weight (bw) per day, corresponding to less than 5% of the acceptable daily intake (ADI) value for

vanillin of 10 mg/kg bw per day established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2002.

The Panel concluded that there would be no safety concern with the proposed use and use level of OSA-VC as a novel food ingredient intended to be used as a source of silicon in food supplements for the adult population as proposed by the applicant.

The Panel concluded that OSA, measured as silicon, is bioavailable following ingestion of OSA-VC and appears similar to values reported in the literature for other established sources of OSA (measured as silicon).

The Panel recommended that the specifications for the novel food ingredient to contain parameters for ethanol, phosphorus and phosphate ion which are residuals from the manufacturing process.

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## 1. Introduction

The present scientific opinion deals with the evaluation of the safety of orthosilicic acid-vanillin complex (OSA-VC) as a novel food ingredient to be used in food supplements as a source of silicon, and with the bioavailability of silicon from the source.

The safety of silicon itself, in terms of amounts that may be consumed, and the consideration of silicon as a nutrient are outside the remit of this Panel.

### 1.1. Background and Terms of Reference as provided by the European Commission

#### 1.1.1. Background

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 are:

- Regulation (EC) No 258/97 of the European Parliament and the Council concerning novel foods and novel food ingredients;<sup>1</sup>
- 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.<sup>2</sup>

The dossier relating to orthosilicic acid-vanillin complex as a source of silicon has been submitted to the Food Safety Authority of Ireland (FSAI), for an initial assessment under Article 6(2) of Regulation (EC) No 258/97 concerning novel foods and novel food ingredients.

On 3 December 2014, FSAI forwarded to the Commission the initial assessment report, concluding that the novel food ingredient meets the requirements of Article 3(1) of Regulation (EC) No 258/97.

On 15 December 2014, the Commission forwarded the initial assessment report to the other Member States. Several Member States submitted comments or raised objections. In consequence, a decision is now required by the Commission under Article 7(1) of Regulation (EC) No 258/97.

In addition, as the requested use of the novel food ingredient is as a source of silicon in food supplements, in order to include orthosilicic acid-vanillin complex in Annex II to Directive 2002/46/EC on food supplements as a source of silicon, the Commission would like to ask EFSA to provide advice both on the safety and bioavailability of the above-mentioned substance.

#### 1.1.2. Terms of Reference

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002,<sup>3</sup> the European Commission asks the European Food Safety Authority to provide a scientific opinion:

- By carrying out the additional assessment for orthosilicic acid-vanillin complex 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 orthosilicic acid-vanillin complex, when added for nutritional purposes to food supplements as a source of silicon and on the bioavailability of silicon from this source, in the context of Directive 2002/46/EC.

## 1.2. Interpretation of the Terms of Reference

The Panel is aware that the mineral silicon (Si) is included in the positive lists of minerals that can be added to foods, including food supplements, as defined by Annex I to Regulation (EC) No 1925/2006<sup>4</sup> and Annex I to Directive 2002/46/EC, respectively. However, data from the scientific literature have established that silicon is typically present in food in the form of OSA which is absorbed from the gastrointestinal tract in humans, and then, silicon is readily excreted in urine. Therefore, in order to

<sup>1</sup> Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. OJ L 43, 14.2.1997, p. 1–6.

<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> 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, 30.12.2006, p. 26–38

address the Terms of Reference of the current mandate and ensure consistency with previous scientific opinions issued on other sources of silicon (EFSA 2009a,b; EFSA ANS Panel, 2016), the Panel considered that bioavailability of OSA from OSA-VC should be the basis for the evaluation of the bioavailability of silicon from that source.

### 1.3. Additional information

#### 1.3.1. Information on existing evaluations and authorisations

##### 1.3.1.1. Silicon

Silicon is an ubiquitous element present in the environment. It is mainly found as insoluble silicates, but small amounts of soluble silicon are naturally present in water, chiefly as orthosilicic acid,  $\text{Si}(\text{OH})_4$  which is the most bioavailable source of silicon.

With respect to the substances currently authorised for use in the manufacture of food supplements as sources of silicon and listed in Annex II of Directive 2002/46/EC, there are choline-stabilised orthosilicic acid (ChOSA), silicon dioxide, silicic acid in the form of gel and organic silicon (monomethylsilanetriol).

The Panel noted that the essentiality of silicon for man has not been established, and a functional role for silicon has not been identified (EFSA, 2004). A recommended intake for silicon has not been set (SCF, 1993; IOM, 2001).

In 2004, EFSA concluded that there were no suitable dose–response data to establish a tolerable upper level (UL) for silicon (EFSA, 2004) and also the Institute of Medicine (IOM) reported that due to lack of data indicating adverse effects of silicon, it was not possible to establish a UL.

The UK Expert group on Vitamins and Minerals (EVM) carried out a risk assessment and set a safe upper level for supplemental daily exposure to silicon at 700 mg Si/day for adults over a lifetime. In terms of elemental silicon, this is equivalent to a safe upper level of 12 mg Si/kg body weight (bw) per day for a 60-kg adult for supplemental silicon (EVM, 2003).

The EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) estimated that the typical dietary intake of 20–50 mg Si/day was unlikely to cause adverse effects (EFSA, 2004).

The NDA Panel has also evaluated a number of health claims related to silicon pursuant to Article 13(1) of Regulation (EC) No 1924/2006<sup>5</sup> (i.e. stimulating macrophages and increasing circulating lymphocytes; protection against aluminium accumulation in the brain; 'cardiovascular health'; forming a protective coat on the mucous membrane of the stomach; neutralisation of gastric acid; contribution to normal formation of collagen and connective tissue; maintenance of normal bone; maintenance of normal joints; maintenance of normal appearance and elasticity of the skin; and contribution to normal formation of hair and nails). On the basis of the data presented, the NDA Panel concluded that a cause and effect relationship had not been established between the consumption of silicon and any of the health claims proposed (EFSA NDA Panel, 2009, 2011).

Silicon dioxide, calcium, magnesium and potassium silicates (E 551–553) are authorised food additives in the European Union (EU) according to Annex II and Annex III to Regulation (EC) No 1333/2008<sup>6</sup> on food additives. Currently, their re-evaluation as food additives is still ongoing as foreseen in Regulation (EC) No 257/2010.<sup>7</sup>

##### 1.3.1.2. Vanillin

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is an organic phenolic aldehyde, the primary natural component of the vanilla bean with significant amounts also made from lignin, a by-product from the wood pulp industry

<sup>5</sup> Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25

<sup>6</sup> Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16–33.

<sup>7</sup> Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19–27.



Vanillin (FL N. 05.018) is authorised for use as a flavouring agent in the EU according to Annex I to Regulation (EU) No 1334/2008.<sup>8</sup>

An acceptable daily intake (ADI) of 10 mg/kg bw per day for vanillin has been set by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1967 and later confirmed in its 2001 re-evaluation as a flavouring (JECFA, 1968, 2002).

JECFA concluded that the intake of vanillin in amounts resulting from its use as flavouring would not be of safety concern (JECFA, 2002).

The EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) re-evaluated vanillin in 2008 and concluded that the no-observed-adverse-effect-level (NOAEL) of 1,000 mg/kg bw per day in a 2-year study in rats was > 100 times the estimated daily intake of vanillin when used as a flavouring substance (EFSA, 2008).

## 2. Data and methodologies

### 2.1. Data

The present evaluation is based on the data on OSA-VC in a newly submitted dossier by the applicant (Documentation provided to EFSA n.1), on the initial assessment performed by FSAI (Documentation provided to EFSA n.2), the comments raised by Member States during the assessment of OSA-VC as a novel food ingredient (Documentation provided to EFSA n.3) and subsequent response by the applicant (Documentation provided to EFSA n.4).

Additional information was sought from the applicant during the assessment process (Documentation provided to EFSA n.5 and n.6).

### 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 from the EFSA Scientific Committee.

The ANS Panel assessed the safety of OSA-VC as a novel food ingredient in line with the principles laid down in Commission Recommendation 97/618/EC.<sup>9</sup> In particular, where it is stated that 'Most of the defined chemical substances can probably be tested for their safety similarly to food additives by utilising conventional methods of safety evaluation as described in the SCF Report No 10,' the Panel considered that to reflect state of the art scientific knowledge and welfare considerations, the reference to SCF Report No 10 should be replaced by the latest existing guidance on the safety evaluation of food additives, namely the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

With respect to the evaluation of bioavailability of the nutrient (Si) from the source OSA-VC, the principles contained in the 'Guidance on submissions for safety evaluation of nutrients or of other ingredients proposed for use in the manufacture of foods' (SCF, 2001) were followed.

Dietary exposure to the nutrient source was estimated based on the proposed uses and use levels in food supplements (see Section 3.3).

## 3. Assessment

### 3.1. Technical data

#### 3.1.1. Identity of the substance

Based on the data provided by the applicant, OSA-VC is described as a complex composed of orthosilicic acid and vanillin (4-hydroxy-3-methoxybenzaldehyde).

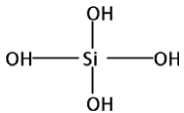
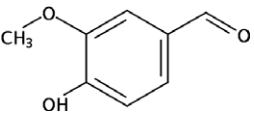
<sup>8</sup> Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354, 31.12.2008, p. 34–50.

<sup>9</sup> Commission Recommendation No 97/618 (EC) concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council (Text with EEA relevance) OJ L 253, 16.09.1997 P. 1–36



Information on the chemical identity of the complex is presented in Table 1 (Documentation provided to EFSA n.1).

**Table 1:** Chemical identity of orthosilicic acid-vanillin complex (OSA-VC) as provided by the applicant (Documentation provided to EFSA n.1)

Name of substance	Orthosilicic acid-vanillin complex (OSA-VC)	
<b>Chemical name</b>	Complex of orthosilicic acid and 4-hydroxy-3-methoxybenzaldehyde (vanillin)	
Trade name	Vanillin-stabilised orthosilicic acid	
Description	A colourless liquid with a characteristic odour and taste (not further defined)	
Solubility	Completely soluble in water	
<b>Identity of the components of the complex</b>	Orthosilicic acid	4-hydroxy-3-methoxybenzaldehyde
Proportion of the components of the complex	Vanillin: silicon=1:1.254	
CAS Number of the components of the complex	10193-36-9	121-33-5
EINECS Number of the components of the complex	233-477-0	204-465-2
Synonyms of the components of the complex	Silicic acid; tetrahydroxysilane; monosilicic acid; silicon tetrahydroxide	Benzaldehyde, 4-hydroxy-3-methoxy-; vanillic aldehyde; <i>p</i> -hydroxy- <i>m</i> -methoxybenzaldehyde; 4-hydroxy- <i>m</i> -anisaldehyde
Chemical formula of the components of the complex	H <sub>4</sub> SiO <sub>4</sub>	C <sub>8</sub> H <sub>8</sub> O <sub>3</sub>
Structural formula of the components of the complex		
Molecular weight of the components of the complex (g/mole)	96.11	152.15

CAS: Chemical Abstracts Service; EINECS: European INventory of Existing Commercial chemical Substances.

### 3.1.1.1. Chemical characterisation of OSA-VC in solution

The Panel noted that monomeric ortho-silicic acid (H<sub>4</sub>SiO<sub>4</sub>) is only stable in highly diluted aqueous solutions. According to data in literature (Martin, 2007), several hydrated forms of ortho-silicic acid exist in aqueous solutions; these include metasilicic acid (H<sub>2</sub>SiO<sub>3</sub>) and tri-silicic acids (H<sub>2</sub>Si<sub>3</sub>O<sub>7</sub>) and their hydrated forms pentahydro-silicic (H<sub>10</sub>Si<sub>2</sub>O<sub>9</sub>) and pyro-silicic acids (H<sub>6</sub>Si<sub>2</sub>O<sub>7</sub>). These substances are derived in reversible equilibrium reactions from orthosilicic acid and are stable in diluted aqueous solutions. During prolonged storage in an acidic environment or when the concentration is increased, the low molecular weight silicic acids undergo further condensation by cross-linking and dehydration. This results in the formation of polysilicic acids chains of variable composition [SiO<sub>x</sub>(OH)<sub>4-2x</sub>] and complex structure.

In its initial application, results from <sup>1</sup>H-NMR and <sup>29</sup>Si-NMR analysis were submitted (Documentation provided to EFSA n.1). In response to comments raised by Member States during their initial assessment (Documentation provided to EFSA n.2), the applicant has performed a re-analysis of the <sup>1</sup>H-NMR spectroscopy.

In order to characterise OSA-VC in aqueous solution, the applicant provided <sup>29</sup>Si-NMR spectra of OSA-VC. From these spectra, it could be concluded that in OSA-VC, the monomeric form Si(OH)<sub>4</sub> prevails; no oligomeric forms were detected at pH 2.4–2.6 and the concentration proposed in the application (Documentation provided to EFSA n.5).

According to the applicant, the interaction between vanillin and orthosilicic acid is difficult to demonstrate due to the weakness of hydrogen bonds. Nevertheless, the applicant has performed <sup>29</sup>Si NMR analysis to examine whether a change in <sup>29</sup>Si signal can be measured between OSA-VC and OSA.

The formation of a complex between OSA and vanillin has been demonstrated by NMR in titration experiments using increasing concentrations of vanillin (Documentation provided to EFSA n.4).

Three different solutions containing 0, 1.07 or 10.7 mg/L of vanillin in the presence of a constant concentration of OSA corresponding to 860 mg/L of silicon (the same concentration as proposed for

OSA-VC). The NMR results showed that increasing vanillin concentrations were accompanied by a left shift in the signal corresponding to OSA. According to the applicant, these data are sufficient to demonstrate the existence of a complex, different from a pH-adjusted solution comprising the two individual components (Document provided to EFSA n.4).

The Panel considered that the analytical data provided by the applicant do not fully support the identity of the material as a complex between OSA and vanillin.

### 3.1.1.2. Particle characteristics of OSA-VC in suspension

The applicant has provided data on particle characteristics of OSA-VC (Documentation provided to EFSA n.1). Four test samples were prepared using a modified method compared to the process described for the manufacturing of the proposed source. In this experiment, increasing amounts of phosphoric acid and potassium silicate were added to a solution of vanillin (fixed concentration) to investigate how the physical aspect of the samples was affected by the potassium silicate concentration. The two samples with the lowest concentration on potassium silicate (i.e. containing the same amount of vanillin and the two lowest concentrations on potassium silicate), remained liquid. However, when analysed by dynamic light scattering (DLS), small particles in suspension into the liquid phase were observed in both samples. The authors stated that most of the particles (in mass) were very small (i.e. between 10 and 20 nm); however, also larger particles, with diameters around 500 nm, were observed in the most diluted sample whereas in the more concentrated sample particles with diameters up to 4,000 nm were observed. The two other samples (i.e. with the highest concentration on potassium silicate) were not analysed by DLS because sedimentation occurred. The Panel noted that the OSA-VC solutions used for this study were not produced using the same manufacturing process detailed in the current application, but by means of a different process. The Panel considered that the particles observed in the two (low concentration) samples were very likely to be aggregates/agglomerates of silica/silicic acid ( $mSiO_2.nH_2O$ ) and that based on the findings from this study, the formation of nanomaterial (e.g. on standing), in the commercial samples of OSA-VC cannot be excluded.

The applicant provided data on the particle size distribution, measured by DLS, of two freshly prepared OSA-VC solutions (not concentrated). (Documentation provided to EFSA n.4). In this subsequent experiment, the samples were produced by adding to a water/ethanol solution of vanillin either a fixed amount of phosphoric acid followed by potassium silicate or a fixed amount of potassium silicate followed by phosphoric acid. Particle size was also measured by transmission electron microscopy (TEM) analysis. TEM observations revealed the presence of different particles in the solution that contained OSA-VC. However, TEM analysis was considered by the applicant of being not appropriate because during the drying of the fresh (liquid) preparations, precipitation of the silicon precursor occurred (Documentation provided to EFSA n.4).

The applicant concluded that, based on DLS analysis, OSA-VC is not a nanomaterial.

The Panel considered that OSA condensates when in solution, and that the particles observed in the two, low concentration samples, are very likely to be aggregates/agglomerates of silica/silicic acid ( $mSiO_2.nH_2O$ ). The formation of nanomaterial, e.g. on standing of the commercial solutions of OSA-VC, cannot therefore be excluded.

### 3.1.2. Proposed specifications

The specifications for OSA-VC as proposed by the applicant are presented in Table 2 (Documentation provided to EFSA n.1, n.5).

**Table 2:** Specifications for OSA-VC as proposed by the applicant (Documentation provided to EFSA n.1, n. 5)

Parameter	Proposed specification	Analytical method
Aspect	Colourless liquid	
Odour	Characteristic	
Taste	Characteristic	
Silicon	681 mg/L < [Si] < 1,233 mg/L	ICP-AES (ISO 11885) <sup>(a)</sup>
Vanillin	854 mg/L < [vanillin] < 1,547 mg/l	GC-FID <sup>(b)</sup>
Acidity (pH)	2.4-2.6	
Benzene	< 1 µg/L	GC-MS (ISO 11423-1)

Parameter	Proposed specification	Analytical method
<b>Heavy metals</b>		
Cadmium	< 0.5 mg/kg	BN 13805; NBN EN 15763) <sup>(c)</sup>
Lead	< 1 mg/kg	
Arsenic	< 1 mg/kg	
Mercury	< 0.1 mg/kg	
<b>Microbiological parameters</b>		
Total viable count for aerobic mesophilic germs	< 10 cfu/mL	ISO1640:2003
Yeasts	< 10 cfu/mL	AOAC 997.02
Moulds	< 10 cfu/mL	AOAC 997.02
<i>Escherichia coli</i>	undetectable/1 mL	AFNOR BRD07/7-12/04
Enterobacteriaceae	undetectable/1 mL	AFNOR 3M-01/06-09/97
<i>Staphylococcus aureus</i>	undetectable/1 mL	ISO 6888-1

GC-MS: gas chromatography–mass spectrometry; cfu: colony forming unit.

(a): Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) based on ISO 11885 (1998).

(b): Silylation and gas chromatography-flame ionisation detector (GC-FID) analysis on a Rescom SE-54, 50 m column.

(c): Inductively coupled plasma-mass spectrometry (ICP-MS) after microwave digestion method (based on NBN EN 13805, NBN EN 15763).

To check compliance with the proposed specifications, the applicant provided analytical data of three independent batches of OSA-VC (Documentation provided to EFSA n.1). The data are presented in Table 3.

**Table 3:** Analysis of three independent batches of OSA-VC as provided by the applicant

Parameter	Proposed specification	Batch 1 (ARD 1320001)	Batch 2 (ARD 1320002)	Batch 3 (ARD 1320003)
Aspect	Conform	Conform	Conform	Conform
Odour	Characteristic	Characteristic	Characteristic	Characteristic
Taste	Characteristic	Characteristic	Characteristic	Characteristic
Silicon	681–1,233 mg/L	1,008 mg/L	975 mg/L	1,007 mg/L
Vanillin	854–1,547 mg/l	1,160 mg/L	1,070 mg/L	1,150 mg/L
Acidity (pH)	2.4–2.6	2.51	2.55	2.59
Water	Not listed	99.4%	99.4%	99.4%
Ethanol	Not listed	Not given	Not given	Not given
Phosphorus	Not listed	943 mg/L	948 mg/L	926 mg/L
Phosphate [PO <sub>4</sub> <sup>3-</sup> ]	Not listed	2470 mg/L	2780 mg/L	2688 mg/L
Cadmium	< 0.5 mg/kg	< 0.1 mg/kg	< 0.1 mg/kg	< 0.1 mg/kg
Lead	< 1 mg/kg	< 0.2 mg/kg	< 0.2 mg/kg	< 0.2 mg/kg
Arsenic	< 1 mg/kg	< 0.4 mg/kg	< 0.4 mg/kg	< 0.4 mg/kg
Mercury	< 0.1 mg/kg	< 0.04 mg/kg	< 0.04 mg/kg	< 0.04 mg/kg
Benzene	< 1 µg/L	< 1 µg/L	< 1 µg/L	< 1 µg/L
Total viable count for aerobic mesophilic germs	< 10 cfu/mL	0 cfu/mL	0 cfu/mL	0 cfu/mL
Yeasts	< 10 cfu/mL	0 cfu/mL	0 cfu/mL	0 cfu/mL
Moulds	< 10 cfu/mL	0 cfu/mL	0 cfu/mL	0 cfu/mL
<i>Escherichia coli</i>	undetectable/1 mL	Absent	Absent	Absent
Enterobacteriaceae	undetectable/1 mL	Absent	Absent	Absent
<i>Staphylococcus aureus</i>	undetectable/1 mL	Absent	Absent	Absent

cfu: colony forming unit.

The Panel noted that, the analytical data provided in support of the proposed specifications contain measures of some parameters (ethanol, phosphorus, phosphate ion) which are not listed in the

proposed specifications. The Panel recommended that these parameters to be added to the proposed specifications.

The Panel considered that the analytical data provided are sufficient to demonstrate conformity with the proposed specifications.

The applicant provided analysed one batch of OSA-VC (Batch ARD 13240001) for the presence of the following mycotoxins: aflatoxin G1, aflatoxin G2, aflatoxin B1, aflatoxin B2, deoxynivalenol, zearalenone, HT2-toxin, T2-toxin, ochratoxin A, fumonisin B1, fumonisin B2, fumonisin B3 and patulin. The results were below the limit of detection of the analytical method used.

### 3.1.3. Manufacturing process

According to information provided by the applicant, to produce OSA-VC, vanillin powder is completely dissolved in 40% ethanol at 40°C. The solution is then diluted by adding water and acidified down to a pH of 1.5–2.5 by adding phosphoric acid. Following this, potassium orthosilicate is dripped into the solution under gentle stirring. The final pH is adjusted to the values in accordance with the proposed specifications. (Documentation provided to EFSA n. 1 and n.4).

Residues of the ethanol (approximately 0.05%) and phosphoric acid (approximately 0.4%) are present in the final product. The Panel noted that no specifications for these residuals have been proposed by the applicant.

According to information provided by applicant, vanillin is produced from guaiacol and glyoxylic acid as starting materials. Guaiacol reacts with glycolic acid by electronic aromatic substitution, resulting in the formation of 3-methoxy-4-mandelic acid (vanillylmandelic acid). Vanillylmandelic acid is further transformed, via oxidative decarboxylation with the formation of 4-hydroxy-3-methoxyphenylglyoxilic acid as intermediate, to vanillin. In this process, a copper, manganese, cobalt mixed oxide is used as a catalyst. Details of these reactions have been described in literature (Kalikar et al., 1986).

The applicant stated that benzene, although used in the synthesis of vanillin (as an extraction solvent for unreacted guaiacol), was not detected in the final product ( $< 1 \mu\text{g/L}$ ).

The Panel noted that in literature other processes for the synthesis of vanillin (Bjørsvik and Minisci, 1999; Araújo et al., 2010; Bandyopadhyay and Banik, 2012) or of vanillin precursors (Fatiadi and Schaffer, 1974; Favier et al., 2002; Favier and Duñach, 2003.) have been described. In these studies, other starting materials or other catalysts for the oxidative decarboxylation of vanillin intermediates have been used. In the present evaluation, only the process of synthesis of vanillin as described above has been evaluated.

### 3.1.4. Methods of analysis in food

The applicant provided reference to analytical methods used to verify that the batches conformed to the proposed specifications.

### 3.1.5. Stability of the substance and reaction and fate in food

#### 3.1.5.1. Long-term stability

The stability of OSA-VC was tested for 24 months at room temperature. No changes were observed in the physical parameters investigated (colour, odour and taste) (Documentation provided to EFSA n.1).

After 24 months, a slight precipitate was observed, which the applicant stated did not affect the quality of the product. No further characterisation of the precipitate was provided. The pH of the solution slightly fluctuated (between pH 2.4 and pH 2.6) over the 24 month period, as were the silicon and vanillin levels as determined by ICP-AES and GC-FID, respectively. Bacteriological analyses did not highlight any effect of time.

The Panel noted that singles measures were conducted at the different time points, thus limiting the validity of this test.

#### 3.1.5.2. Effect of temperature on stability

An accelerated stability test was also conducted after storing the product at 40°C for a period of 6 months (Documentation provided to EFSA n.1).

No changes were observed in the physical parameters investigated (appearance, colour, odour and taste) whereas pH, vanillin and silicon concentrations were not measured.

The Panel noted that singles' measures were conducted at different time points, thus limiting the validity of this test.

## 3.2. Proposed uses and use levels

The applicant requests the inclusion of OSA-VC as a source of silicon in food supplements under the provisions of Directive 2002/46/EC.

The OSA-VC supplement solution is prepared according to the manufacturing process as described above and it is proposed to be used in a standard dose of 15 mL/day of dietary supplement (containing 98.9% OSA-VC complex), equivalent to 14.8 mL OSA-VC and providing 10.1–18.2 mg silicon/day.

According to the applicant, this product is intended to be used only in the adult population and it is not intended for children (Documentation provided to EFSA n.4).

## 3.3. Exposure estimate

According to the applicant, the proposed use of OSA-VC in food supplements would lead to an intake of 10–18 mg/day Si in adults. In addition to the average dietary intake of 20–50 mg/day (EFSA, 2004), the anticipated total intake of Si from the proposed use and use levels of OSA-VC would be approximately 30–70 mg/day.

The maximum vanillin intake resulting from the consumption of OSA-VC would be approximately 12–23 mg/day, corresponding to less than 0.5 mg/kg bw per day for adults. The Panel noted that this would be less than 5 % of the ADI value for vanillin established by JECFA (JECFA, 2002).

## 3.4. Biological and toxicological data

The applicant has provided evidence that under the conditions of simulated intestinal digestion (pH 6.8) OSA and vanillin are not associated in a complex.

The NMR data on OSA-VC indicated that there was no covalent bond between vanillin and orthosilicic acid. Both compounds are linked only by weak electrostatic interactions (hydrogen bonds). Vanillin and orthosilicic acid are linked only at acid pH (pH = 2.4–2.6) (Documentation provided to EFSA n.1 and n.5). As already stated previously for another similar substance (EFSA, 2009a) and based on the NMR data provided for OSA-VC, the Panel considered that Si–C or Si–O–C covalent bonds are not found in OSA-VC.

Moreover, the applicant provided results from an experiment aimed at verifying whether OSA-VC was modified under the conditions of simulated intestinal digestion (pH 6.8) in the absence of digestive enzymes. Three solutions were analysed by NMR of <sup>29</sup>Si at natural abundance: one containing OSA-VC, a second one with OSA alone and the third one being the simulated intestinal digestion fluid used as a control (Documentation provided to EFSA n. 5).

A shift in the <sup>29</sup>Si signal was measured between OSA-VC (–73.30 ppm) and OSA (–73.28 ppm). The incubation of OSA-VC at pH 6.8 (simulated intestinal digestion) induced a similar shift in the <sup>29</sup>Si signal (–73.27 ppm). According to the applicant, these results can be interpreted as a modification of the interaction between OSA and vanillin. The Panel noted that the similarity in the <sup>29</sup>Si signal measured for the solution containing OSA alone and the solution of OSA-VC after intestinal digestion could be interpreted as a lack of interaction between OSA and vanillin after intestinal digestion.

In the light of the above, the Panel considered that at pH 6.8, OSA and vanillin would not be in a complex form.

The Panel was therefore of the opinion that no additional toxicological data were required for the complex, rather based its conclusions on the information available for its two components, OSA and vanillin.

### 3.4.1. Absorption, distribution, metabolism and excretion

#### 3.4.1.1. Introduction

Silicon occurs as silicon dioxide (SiO<sub>2</sub>) or the corresponding silicic acids formed by the hydration of the oxide. OSA [Si(OH)<sub>4</sub>] is the simplest acid and the main chemical species of silicon soluble in water (Carlisle, 1982). OSA is accepted as being the natural biological form of silicon in humans and animals and plays a major role in delivering silicon to the living cells (Reffitt et al., 1999; Jugdaohsingh et al., 2000, 2002; Sripanyakorn et al., 2009; Jurkić et al., 2013). The availability of silicon from a given source depends on the solubility or speciation of the compound concerned (Van Dyck et al., 1999).



### 3.4.1.2. Bioavailability of silicon from OSA-VC

In the context of this opinion, the term bioavailability is used to indicate systemic availability of OSA from OSA-VC.

The applicant has submitted results from a single-centre, double-blind, cross-over, randomised, placebo-controlled trial, conducted according Good Clinical Practices (GCP) guidelines (Documentation provided to EFSA n.1), later published as Marcowycz et al. (2015). Additional supporting information was made available to EFSA (Documentation provided to EFSA n. 6).

The primary objective of the study was to measure plasma concentration time profile as a surrogate for absorption of silicon after ingestion of OSA-VC solution (15 mL solution at pH 2.5, containing 44 mg OSA-VC and corresponding to 12.8 mg silicon) compared to a placebo.

In addition, urinary excretion of silicon was also assessed, since it correlates to the dietary intake of silicon and as such it was used as a proximal measure of absorption.

The study was conducted in 14 healthy subjects (5 men and 9 women, aged 18–39); the sample size was calculated to obtain a 90% power to demonstrate a difference of 32577  $\mu\text{g}\cdot\text{min}/\text{L}$  in the area under the curve (AUC) values between treated and control and increased to account for possible dropouts. The intention-to-treat population (ITT,  $n = 14$ ) was eventually the same as the per protocol (PP,  $n = 14$ ) since none of the subjects terminated the study early.

The subjects were randomly assigned to the one of the two sequences of treatments (OSA-VC followed by placebo or placebo followed by OSA-VC). Instructions were also given to avoid smoking, consumption of alcohol and of foods rich in silicon and to limit physical exercise on the day before each of the two experimental sessions. Subjects were in a fasting state when receiving the intervention.

Blood samples were collected at baseline ( $T_0$ ), immediately prior to the ingestion of either OSA-VC or placebo, and at 30-minute intervals for the first 3 hours ( $T_{30}$ ,  $T_{60}$ ,  $T_{90}$ ,  $T_{120}$ ,  $T_{150}$  and  $T_{180}$ ) and then every 2 hours ( $T_{240}$ ,  $T_{360}$ ) until the end of the session.

Urine was collected from the subjects on the morning of the experimental session and used as the control to assess silicon excretion. Two additional collections were made at 3-hour intervals ( $T_0$ – $T_{180}$  and  $T_{180}$ – $T_{360}$ ).

The concentration of silicon was measured both in the OSA-VC liquid supplement and in the placebo and was 951 mg/L and 0.51 mg/L, respectively.

The absence of silicon contamination was verified by the authors for all the materials used for the collection of biological samples.

The AUC of plasma Si values between baseline and the end of the experiment ( $\text{AUC}_{T_0-T_{360}}$ ) was measured as the primary endpoint of the study and analysed in both ITT and PP populations using a mixed model analysis of covariance (ANCOVA) for repeated measurements.

Urinary excretion was the secondary endpoint used, and data were analysed in both ITT and PP populations using analysis of variance (ANOVA) model for repeated measurements.

At baseline, plasma Si concentration values were similar: 89.8 (40.1)  $\mu\text{g}/\text{L}$  before consumption of placebo, 82.7 (39.8)  $\mu\text{g}/\text{L}$  before consumption of OSA-VC.

After ingestion of OSA-VC, plasma Si concentration increased up to 155.9 (27.8)  $\mu\text{g}/\text{L}$  at  $T_{90}$  and 156.1 (38.5)  $\mu\text{g}/\text{L}$  at  $T_{150}$ . At the end of the 6-hour session, plasma Si concentration declined without returning to its baseline value.

A statistically significant increase was observed in Plasma Si  $\text{AUC}_{T_0-T_{360}}$  of the subjects taking the supplement OSA-VC compared to placebo.

Urinary Si excretion was also similar between the two groups at baseline and significantly increased already in the first 3 hours after OSA-VC ingestion and after the second 3-hour period ( $T_0$ – $T_{180}$  and  $T_{180}$ – $T_{360}$ ) accounting for 21.1% of the ingested Si dose. The authors noted that this value is lower compared to the typical excretion rate (43–50%) commonly observed after OSA ingestion by other authors (Reffitt et al., 1999; Sripanyakorn et al., 2004, 2009) and comparable with values previously reported for choline stabilised OSA (Sripanyakorn et al., 2009).

The Panel noted that the measurements were of plasma silicon and not OSA, and that no information was provided on the form of silicon in the plasma.

According to the applicant, the results from this single study are in accordance with previous studies on the absorption of silicon from different silicon sources (Popplewell et al., 1998; Sripanyakorn et al., 2009) and previous EFSA opinions (EFSA, 2009a,b, EFSA ANS Panel, 2016).



The Panel considered the study demonstrated that OSA, measured as silicon (form of silicon not determined), is bioavailable following ingestion of OSA-VC and appears similar to values reported for other OSA sources measured as silicon in the literature.

### 3.4.2. Toxicological data

#### 3.4.2.1. Acute toxicity

The applicant submitted data from an acute toxicity study in rats (Documentation provided to EFSA n.1).

The Panel noted that the study had severe limitations owing to the technical difficulties with the dosing of the substance.

The Panel was however of the view that no additional acute toxicity data were required for the complex, rather based its conclusions on the information available for its two components, OSA and vanillin (see Section 1.3.1).

#### 3.4.2.2. Short-term and subchronic toxicity

The applicant submitted data from a 90-day toxicity study in rats (Documentation provided to EFSA n.1).

The Panel noted that the study had severe limitations and did not comply with the OECD TG 408 due to limited number of animals and only one sex tested.

The Panel was however of the view that no additional 90-day toxicity data were required for the complex, rather based its conclusions on the information available for its two components, OSA and vanillin (see Section 1.3.1).

#### 3.4.2.3. Genotoxicity

The applicant submitted data from a bacterial reverse mutation assay (Documentation provided to EFSA n.1).

The Panel noted that the study had severe limitations owing to the technical difficulties with the solubility of the substance.

The Panel was however of the view that no additional genotoxicity data were required for the complex, rather based its conclusions on the information available for its two components, OSA and vanillin (see section 1.3.1).

Vanillin was negative in valid *in vitro* studies for the induction of gene mutations in bacteria (Ames test) and chromosomal aberrations in mammalian cells, and in a limited *in vivo* oral micronucleus test in mouse bone marrow (EFSA, 2008). Based on the weight of evidence available from *in vitro* and *in vivo* studies on vanillin and structurally related substances, the AFC Panel concluded that vanillin and substances belonging to the same Flavouring Group Evaluation (FGE.20) did not raise concern with respect to genotoxicity (EFSA, 2008).

Concerning OSA, the Panel noted that silica is considered not to be genotoxic *in vitro* or *in vivo* (IARC, 1987).

## 3.5. Discussion

The European Commission asked EFSA to provide a scientific opinion on the safety of OSA-VC as a novel food ingredient to be included in Annex II to Directive 2002/46/EC as an authorised substance which may be used in the manufacture of food supplements and on the bioavailability of silicon from this source. The safety of silicon in terms of the amounts that may be consumed is outside the remit of this Panel.

In 2004, EFSA concluded that there were no suitable dose–response data to establish an upper level for silicon and also the IOM reported that due to lack of data indicating adverse effects of silicon, it was not possible to establish a UL. EFSA estimated that a typical dietary intake of 20–50 mg Si/day per person would be unlikely to cause adverse effects (EFSA, 2004). A safe upper level of supplemental silicon intake of 700 mg/day of Si for adults was set by the UK Expert Group on Vitamins and Minerals (EVM, 2003).

The applicant proposed the use of OSA-VC supplement solution in a standard dose of 15 mL/day of dietary supplement (containing 98.9% OSA-VC complex), equivalent to 14.8 mL OSA-VC. The proposed use is limited to the adult population and not intended for children.

The daily consumption of OSA-VC at the daily dose recommended by the applicant would provide a supplemental intake of silicon of approximately 10–18 mg/day which would result in an estimated total intake from supplement use and from the diet of roughly 30–70 mg silicon/day, thus not exceeding the safe upper level of supplemental silicon intake of 700 mg/day of Si for adults as set by the EVM in 2003.

The maximum vanillin intake resulting from the consumption of OSA-VC would be less than 0.3 mg/kg bw per day, corresponding to less than 5% of the ADI value for vanillin of 10 mg/kg bw per day established by JECFA in 2002.

OSA-VC is described by the applicant as a colourless liquid with a characteristic odour and taste (not further defined) with a pH of 2.4–2.6.

The applicant has provided evidence that the two components of the complex are linked by electrostatic bonds and that the complex is stable only in an acidic environment.

With respect to the results from the stability tests of OSA-VC, the Panel noted that single measurements of pH, Si and vanillin made at the different time points did not show significant variations from the proposed specifications. The Panel considered that there would be no safety implications if the complex disassociated over time but that this could decrease the bioavailability of silicon from the proposed source OSA-VC.

The applicant has demonstrated that under the conditions of simulated intestinal digestion (pH 6.8) and in the absence of digestive enzymes, the complex between OSA and vanillin is dissociated.

The Panel was therefore of the opinion that no additional toxicological data were required and based its conclusions on the information available for its two components, OSA and vanillin.

With respect to the bioavailability of silicon from OSA-VC, the Panel acknowledged that this has been demonstrated only in a single randomised, placebo-controlled, cross-over study conducted in 14 healthy subjects administered either 15 mL of OSA-VC solution or placebo. Plasma Si levels were used as a surrogate for absorption and measured at baseline and at different intervals within a period of 6 hours. Urinary Si excretion was also measured as a secondary endpoint, at baseline and after 3 and 6 hours from ingestion of either the supplement or placebo. The study demonstrated a significant increase in the plasma Si concentration, with maximum concentrations achieved within 3 hours from intake of supplemental Si. Urinary excretion in the 6-hour period accounted for 21.1% of the ingested Si dose and also in this case significantly different from the placebo group.

The Panel considered the study demonstrated that OSA, measured as silicon (form of silicon not determined), is bioavailable following ingestion of OSA-VC and the bioavailability appears similar to that reported in the literature for other OSA sources.

## 4. Conclusions

The Panel concluded that there would be no safety concern with the proposed use and use level of OSA-VC as a novel food ingredient intended to be used as a source of silicon in food supplements for the adult population as proposed by the applicant.

The Panel concluded that OSA, measured as silicon, is bioavailable following ingestion of OSA-VC and appears similar to values reported in the literature for other established sources of OSA (measured as silicon).

## 5. Recommendations

The Panel recommended that the specifications for the novel food ingredient to contain parameters for ethanol, phosphorus and phosphate ion which are residuals from the manufacturing process.

### Documentation provided to EFSA

- 1) Dossier 'Application for the approval of an orthosilicic acid – vanillin complex for use as a novel food ingredient and addition to the list of authorised vitamin and mineral forms in Directive 2002/46/EC'. February 2014. Additional data provided on 25 June 2014 and 1 March 2016. Submitted by Nutraveris on behalf of Eytelia sprl (formerly Dexsil Labs).
- 2) Initial assessment report carried out by Food Safety Authority Ireland (FSAI): 'Safety Assessment of Orthosilicic acid-vanillin complex (OSA-VC)'. December 2014.
- 3) Member States comments and objections. February 2015.
- 4) Response by the applicant to the initial assessment report and the Member States' comments and objections. Submitted by Nutraveris on behalf of Eytelia sprl (formerly Dexsil Labs). 29 October 2015.

- 5) Additional information. April 2017. Submitted by Nutraveris on behalf of Eytelia sprl (formerly Dexsil Labs) in response to a request from EFSA.
- 6) Additional information. September 2017. Submitted by Nutraveris on behalf of Eytelia sprl (formerly Dexsil Labs) in response to a request from EFSA.

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## Abbreviations

ADI	acceptable daily intake
AFC	EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ANS	The Panel on Food Additives and Nutrient Sources added to Food
AUC	area under the curve
bw	body weight

CAS	Chemical Abstracts Service EINECS: European INventory of Existing Commercial chemical Substances
cfu	colony forming unit
ChOSA	choline-stabilised orthosilicic acid
DLS	dynamic light scattering
EINECS	European INventory of Existing Commercial chemical Substances
EVM	UK Expert group on Vitamins and Minerals
FAO	Food and Agriculture Organization of the United Nations
FGE	Flavouring Group Evaluation
FSAI	Food Safety Authority of Ireland
GC-FID	gas chromatography-flame ionisation detector
GC-MS	gas chromatography-mass spectrometry
GCP	Good Clinical Practices
ICP-AES	inductively coupled plasma-atomic emission spectroscopy
ICP-MS	inductively coupled plasma-mass spectrometry
IOM	Institute of Medicine
ITT	intention-to-treat population
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NMR	nuclear magnetic resonance
NOAEL	no-observed-adverse-effect-level
OECD	Organisation for Economic Co-operation and Development
OSA	orthosilicic acid
OSA-VC	orthosilicic acid-vanillin complex
PP	per protocol
TEM	transmission electron microscopy
UL	Tolerable Upper intake level
WHO	World Health Organization