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Assessment of the application for renewal of authorisation of selenomethionine produced by *Saccharomyces cerevisiae* CNCM I-3060 (selenised yeast inactivated) for all animal species

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Abstract

The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the application for renewal of authorisation of organic form of selenium produced by *Saccharomyces cerevisiae* CNCM I-3060 (selenised yeast inactivated) (Sel-Plex[®]) for all animal species. In 2006, the FEEDAP Panel delivered an opinion on the safety and efficacy of the additive; subsequently it was authorised in the EU. The evidence provided indicates that the additive currently in the market complies with the conditions of authorisation. No new evidence was found that would make the FEEDAP Panel reconsidering its previous conclusions in the safety for target species, consumers and environment. In particular, the Panel confirms that the use of Sel-Plex[®] in animal nutrition does not pose a risk to consumers provided that the maximum selenium supplementation of 0.2 mg/kg feed from Sel-Plex[®] is not exceeded, yet respecting the maximum total selenium in feed of 0.5 mg/kg. In the context of the current application, the Panel reviewed toxicological studies; based on two repeated-dose studies on rats and dogs, it is concluded that the toxic potential of Sel-Plex[®] is only related to its selenium content. New data on characterisation of the additive and studies on effects on skin and eyes led the Panel reconsider the safety for the user. The Panel concluded that the additive is hazardous upon inhalation and a likely respiratory sensitiser; owing to the high dusting potential, persons handling the additive are at risk by inhalation. It is considered not irritant to the eyes and skin. A recommendation regarding the denomination of the additive under assessment was proposed by the Panel.

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Keywords: nutritional additive, compounds of trace elements, selenium, selenised yeast, *Saccharomyces cerevisiae* CNCM I-3060, Sel-Plex[®], safety

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Table of contents

Abstract.....	1
1. Introduction.....	4
1.1. Background and Terms of Reference.....	4
1.2. Interpretation of the Terms of Reference.....	4
1.3. Additional information.....	4
2. Data and methodologies.....	4
2.1. Data.....	4
2.2. Methodologies.....	5
3. Assessment.....	5
3.1. Characterisation.....	5
3.1.1. Characterisation of the additive.....	5
3.1.2. Characterisation of the production strain.....	6
3.1.3. Physical characteristics of the product.....	6
3.1.4. Stability and homogeneity.....	7
3.1.5. Conditions of use.....	7
3.2. Safety.....	7
3.2.1. Absorption, distribution, metabolism and excretion (ADME).....	7
3.2.2. Toxicological studies.....	7
3.2.2.1. Genotoxicity studies.....	8
3.2.2.2. Repeated-dose toxicity studies.....	8
3.2.3. Safety for the target species.....	8
3.2.4. Safety for the consumer.....	9
3.2.4.1. Conclusions on safety for the consumer.....	9
3.2.5. Safety for the user.....	9
3.2.5.1. Effects on the respiratory system.....	9
3.2.5.2. Effects on eyes and skin.....	10
3.2.5.3. Conclusions on safety for the user.....	10
3.2.6. Safety for the environment.....	10
3.3. Post-market monitoring.....	10
4. Conclusions.....	10
5. Recommendations.....	11
Documentation provided to EFSA.....	11
Chronology.....	11
References.....	11
Abbreviations.....	12
Annex A – Selenium speciation of SEL-PLEX® aqueous fraction.....	13

1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003¹ establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 14(1) of that Regulation lays down that an application for renewal shall be sent to the Commission at the latest one year before the expiry date of the authorisation.

The European Commission received a request from Alltech Ireland² for renewal of the authorisation of selenomethionine produced by *Saccharomyces cerevisiae* CNCM I-3060 (selenised yeast inactivated), when used as a feed additive for all animal species (category: nutritional additives; functional group: compounds of trace elements).

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 14(1) (renewal of the authorisation). The particulars and documents in support of the application were considered valid by EFSA as of 11 April 2016.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and the efficacy of the product organic form of selenium produced by *Saccharomyces cerevisiae* CNCM I-3060 (selenised yeast inactivated), when used under the proposed conditions of use (see Section 3.1.5).

1.2. Interpretation of the Terms of Reference

The application for renewal of the authorisation does not include a proposal for amending or supplementing the conditions of the original authorisation that would have an impact on the efficacy of the additive; therefore efficacy is not assessed. The present opinion will focus only on the safety aspects.

1.3. Additional information

The FEEDAP Panel has adopted two opinions on the safety and efficacy of Sel-Plex[®]2000, consisting of selenised yeast produced by *S. cerevisiae* CNCM I-3060 (EFSA, 2006; EFSA FEEDAP Panel, 2011).

Selenomethionine (organic form of selenium produced by *S. cerevisiae* CNCM I-3060) is authorised as a nutritional additive for all animal species.^{3,4}

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier⁵ in support of the authorisation request for the use of organic form of selenium produced by *S. cerevisiae* CNCM I-3060 (Selenised yeast inactivated) as a feed additive. The technical dossier was prepared following the provisions of Article 14 of Regulation (EC) No 1831/2003, Regulation (EC) No 429/2008⁶ and the applicable EFSA guidance documents.

¹ Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

² Alltech Ireland, Sarney, Summerhill Road, A86 X006 Dunboyne, Co. Meath, Ireland.

³ Commission Regulation (EC) No 1750/2006 of 27 November 2006 concerning the authorisation of selenomethionine as a feed additive. OJ L 330, 28.11.2006, p. 9.

⁴ Commission Implementing Regulation (EU) No 427/2013 of 8 May 2013 concerning the authorisation of selenomethionine produced by *Saccharomyces cerevisiae* NCYC R646 as a feed additive for all animal species and amending Regulations (EC) No 1750/2006, (EC) No 634/2007 and (EC) No 900/2009 as regards the maximum supplementation with selenised yeast. OJ L 127, 9.5.2013, p. 20.

⁵ FEED dossier reference: FAD-2015-0046.

⁶ Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

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

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment are valid and applicable for the current application.⁷

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of selenomethionine produced by *Saccharomyces cerevisiae* CNCM I-3060 (Selenised yeast inactivated) is in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance document: Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2013).

3. Assessment

This assessment regards the renewal of the authorisation of the additive, organic form of selenium produced by *S. cerevisiae* CNCM I-3060 (selenised yeast inactivated), as a nutritional additive (functional group: compounds of trace elements) for all animal species. The additive is authorised as organic form of selenium produced by *S. cerevisiae* CNCM I-3060 and characterised as organic selenium mainly selenomethionine (SeMet) (63%) and low molecular weight selenocomponents (34–36%), with a content of 2,000–2,400 mg Se/kg (97–99% of organic selenium). The maximum selenium supplementation rate is 0.2 mg from Sel-Plex[®]/kg complete feed.

The species *S. cerevisiae* is considered by EFSA to be suitable for the Qualified Presumption of Safety (QPS) approach to safety assessment (EFSA, 2007; EFSA BIOHAZ Panel, 2013). This approach requires the identity of the strain to be conclusively established and evidence that the strain does not show resistance to antibiotics of human and veterinary importance.

3.1. Characterisation

The applicant stated that no changes in the manufacturing process and in the composition/properties of the additive have been introduced since the additive is authorised.

3.1.1. Characterisation of the additive

Analytical data on the composition of the additive were provided for three batches. On average, total selenium content was 2,273 mg/kg additive (range 2,143–2,433), selenium from SeMet 1,449 mg/kg (range 1,342–1,609) – corresponding to 63.7% of total selenium (specification \geq 63%) – and selenium from selenocysteine (SeCys) 65 mg/kg (range 42–88). Inorganic selenium content was very low: average value for Se(IV) was 3.3 mg/kg (range 2.8–3.6) while Se(VI) was in all cases below the limit of quantification (LOQ = 1 mg/kg).⁸ The data show compliance with those reported in the characterisation of the additive in the authorising Regulation (Regulation (EC) No 1750/2006).⁹

The applicant provided further data on speciation of the unidentified selenocompounds which account \approx 35% of the active substance of the additive.¹⁰ Thus, using inductively coupled plasma mass spectrometry (ICP-MS) and complementary reversed-phase/hydrophilic ion interaction liquid chromatography–electrospray hybrid quadrupole trap/orbitrap mass spectrometry, 64 selenometabolites were detected in the aqueous fraction (\approx 15%) of one batch of the additive (see Annex A). The selenometabolome of Se-rich yeast aqueous fraction is principally constituted of selenoethers (14 compounds), conjugates of SeCys containing di- and tripeptides (28 species) and occasionally present selenols and selenoxides. None of the identified selenocompounds had a concentration higher than 46 mg Se/kg (1.7% of the total selenium content).

In summary, the mean values would indicate that total selenium of the additive consists of approximately 64% SeMet, 15% of water-soluble selenometabolites, 20% of unknown selenium species;

⁷ The report linked to the previous dossier (related to EFSA-Q-2005-071) is available on the EURL website: <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2005-0007.pdf>

⁸ Technical dossier/Section II/Annex II_1_3.

⁹ Organic selenium mainly selenomethionine (63%) and low molecular weight selenocomponents (34–36%) content of 2,000–2,400 mg Se/kg (97–99% of organic selenium).

¹⁰ Technical Dossier/Supplementary Information (November 2016).

the additive also contains, in another order of magnitude, a small quantity of SeCys (65 mg/kg) and inorganic Se(IV) and Se(VI) (< 3.6 mg/kg).

Analysis of three batches of the additive resulted in a moisture content of 4.5–5.6%, crude protein 45.8–48.1%, nitrogen-free extract 33.3–37.0%, crude fat 6.3–7.1% and crude ash 5.0–6.2%.¹¹ The same batches were analysed for impurities.¹¹ Content of lead, cadmium, mercury and arsenic were < 0.030 mg Pb/kg, < 0.008 mg Cd/kg, < 0.002 mg Hg/kg and < 0.337 mg As/kg additive. Levels of dioxins and the sum of dioxins plus dioxin-like PCBs were 0.092 ng WHO-PCDD/F-TEQ per kg and 0.100 ng WHO-PCDD/F-PCB-TEQ per kg. These values comply with the thresholds set in Directive 2002/32/EC¹² for compounds of trace elements or, if not mentioned in the Directive, do not represent a concern.

The applicant also provided analytical data for the same batches as above on mycotoxins and microbial contamination.¹¹ The following mycotoxins were investigated: tricothecenes (deoxynivalenol, toxin HT-2, toxin T-2), fumonisins (fumonisin B1 and fumonisin B2), zearalenone, aflatoxins (aflatoxin B1, aflatoxin B2, aflatoxin G1, aflatoxin G2) and ochratoxin A; levels were always below the limit of detection (LOD).¹³ Data on microbiological contamination included: total aerobic count (< 10 cfu/g), total coliforms (< 10 cfu/g), *Escherichia coli* β -glucuronidase positive (< 10 cfu/g), positive coagulase staphylococci (< 10 cfu/g), *Salmonella* spp. (absence in 25 g), *Pseudomonas* spp. (< 50 cfu/g), anaerobic sulfate reducers (< 10 cfu/g), *Clostridium perfringens* (< 10 cfu/g), moulds (< 10 cfu/g) and yeasts (< 10 cfu/g).

3.1.2. Characterisation of the production strain

The additive 'organic form of selenium (selenised yeast inactivated)' is produced by a strain of *Saccharomyces cerevisiae*, which is deposited at the French Collection Nationale de Cultures de Microorganismes (CNCM) with accession number CNCM I-3060.¹⁴ This strain is naturally occurring and is not genetically modified.¹⁵ The strain was identified as *S. cerevisiae* by 26S rDNA D1/D2 sequence analysis.¹⁶

The FEEDAP Panel notes that the Se-metabolic profile (see Section 3.1.1) is characteristic of the specific yeast strain used and the fermentation parameters of its given product (Fagan et al., 2015).

The production strain is deposited since 24 June 2003 at the 'Collection Nationale de Cultures de Microorganismes, (CNCM)' in France; the certificate of deposition was provided.¹⁷

3.1.3. Physical characteristics of the product

The active substance is a free-flowing powder, water dispersible, with an apparent density of 0.74 ± 0.03 g/L.¹⁸

Actual data on particle size distribution of three batches of the additive showed that particles < 10 μ m averaged 1.97% (range 0.95–3.62), < 50 μ m 26.97% (range 20.86–36.23) and < 100 μ m 65.01% (range 55.64–74.12).¹⁹ The dusting potential, measured with the Stauber–Heubach method, averaged 3,000 mg/m³ (range 1,815–4,785).²⁰

The direct comparison of these data with that referred in the first Sel-Plex[®] opinion (EFSA, 2006) misses some issues, namely that the current data covers smaller particles (< 10 μ m and < 50 μ m) and that the measure units of dusting potential are different (mg/50 g sample vs mg dust/m³). Nevertheless, taking into account that no changes in the manufacturing process were identified and that particle size distribution are comparable with data previously reported (87% below 0.1 mm) (EFSA, 2006), no impact on physical state of the product is expected.

¹¹ Technical Dossier/Section II/ Annex II_1_5.

¹² Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed. OJ L 140, 30.5.2002, p. 10.

¹³ Reported LODs. Tricothecens: deoxynivalenol, LOD = 0.020 mg/kg; toxin HT-2 and T-2, LOD = 0.010 mg/kg. Fumonisins: B1 and B2, LOD = 0.010 mg/kg. Zearalenone, LOD = 0.010 mg/kg. Aflatoxins: B1, B2, G1 and G2, LOD = 0.0005 mg/kg. Ochratoxin A, LOD = 0.0010 mg/kg.

¹⁴ Technical Dossier/Supplementary Information February 2017/Annex I.

¹⁵ Technical Dossier/Section II/Annex II_2_2.

¹⁶ Technical Dossier/Supplementary Information February 2017/Annex II.

¹⁷ Technical Dossier/Supplementary Information (February 2017)/Annex I.

¹⁸ Technical Dossier/Section II.

¹⁹ Technical Dossier/Supplementary Information (December 2016)/Annex 1.

²⁰ Technical Dossier/Supplementary Information (December 2016)/Annex 2.

3.1.4. Stability and homogeneity

For compounds of trace elements, stability studies are generally not required.

In addition, no changes in the manufacturing process were identified and any impact on stability and homogeneity is not expected. Therefore, data from the previous submission and technical dossier can still be considered valid and can be used to confirm the shelf-life of the additive itself, of the additive in pre-mixtures and of the additive in feeds.²¹

3.1.5. Conditions of use

The additive is intended to be used for all animal species/categories up to a total of 0.2 mg Se from Sel-Plex[®]/kg complete feeds (12% moisture), being the maximum total selenium content in complete feed shall be of 0.5 mg/kg. This is in agreement with the provision of the Regulation authorising the additive. The additive is to be incorporated into feed in the form of a premixture.

The current authorisation includes under other provisions some measures for the protection of the user: breathing protection, safety glasses and gloves should be worn by the user during the handling of the additive.

3.2. Safety

In the view of the FEEDAP Panel, the identity of the strain having being established (see Section 3.1.2), *S. cerevisiae* CNCM I-3060 is considered by EFSA to be suitable for the QPS approach to safety assessment (EFSA, 2007; EFSA BIOHAZ Panel, 2013), and consequently, is presumed safe for the target species, consumers of products from animals fed the additive and the environment.

Following the requirements for applications concerning renewals of an authorisation, the applicant provided data aiming to demonstrate that, in the light of the current knowledge, the additive remains safe for target species, consumers, users/workers and the environment under the approved conditions.²²

The applicant has in place a non-conformance reporting system, which collates and documents all non-conformances associated with Sel-Plex[®], among other products. The applicant stated that there have been no reports of any adverse effects including accidents to target animals, consumers, users and the environment.

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

In its opinion of 2006, the FEEDAP Panel described the absorption of SeMet in monogastric and ruminants as well as its metabolism and excretion (EFSA, 2006). In 2011, the FEEDAP Panel delivered another opinion on Sel-Plex[®] concluding that SeMet has a higher absorption and tissue deposition than inorganic selenium compounds such as sodium selenite (EFSA FEEDAP Panel, 2011).

After the 2011 opinion, the enhanced bioaccessibility of SeMet, as compared to Se(VI), Se (IV) and methylselenocysteine was confirmed in an *in vitro* transwell system using Caco-2 cells (Thiry et al., 2013). Also, a study with Sel-Plex[®] confirms a good absorption of selenium by rainbow trout (Pacitti et al., 2015). Burk and Hill (2015) reviewed and discussed the recent advances of knowledge on SeMet metabolism, pointing to the role of selenoprotein P (Sepp1), which is synthesised by the liver and transports selenium to plasma and consequently to the whole organism. Extrahepatic tissues uptake selenium primarily by endocytosis of Sepp1 mediated by the receptors apoER2 and megalin. Expression of apoER2 determines the selenium uptake by most tissues; megalin mediates selenium uptake by kidney cells. One main metabolite, selenosugar (1 β -methylseleno-*N*-acetyl-D-galactosamine) seems to act as a selenium reservoir in tissues.

The FEEDAP Panel concludes that new scientific evidence does not introduce essential changes in the ADME assessment of SeMet.

3.2.2. Toxicological studies

The toxicology of selenium has been reviewed by the European Medicines Agency (EMA, 2015), as well as by Alexander (2015).

²¹ Technical Dossier/Section II/Annexes II_4_1-23.

²² Technical Dossier/Supplementary Information (November 2016)/Annexes 1, 2, 3, 4 and 5.

3.2.2.1. Genotoxicity studies

In the EFSA opinion of 2006 (EFSA, 2006), the genotoxicity of Sel-Plex[®] was assessed. Based on a battery of three studies (bacterial reverse mutation test in *Salmonella* Typhimurium, a mammalian chromosomal aberration test in cultured human lymphocytes and a bone marrow micronucleus test), the Panel could conclude that Sel-Plex[®] is unlikely to have any genotoxic potential. The studies evaluated were further described in the publication of Griffiths et al. (2006a) reporting the same results. The FEEDAP Panel therefore maintains the conclusion drawn in its previous opinion on Sel-Plex[®].

3.2.2.2. Repeated-dose toxicity studies

Regarding repeated-dose toxicity, in its previous assessment, the FEEDAP Panel was not able to reach a conclusion on the sub-chronic toxicity of Sel-Plex[®], based on studies performed on rats (90 days)²³ and dogs (90 days).²⁴ While the dog report appeared complete, the rat one was made available as a preliminary report.

In the course of the renewal evaluation, the FEEDAP Panel evaluated a published study with the data of the same toxicity studies submitted in the previous Sel-Plex[®] dossier (Griffiths et al., 2006b). Briefly, Sel-Plex[®] was given to Sprague–Dawley rats (10 males and 10 females per group) by dietary admixture at concentrations corresponding to 0, 114, 179 and 303 mg Sel-Plex[®]/kg body weight (bw) day (equivalent to 0, 0.23, 0.36 and 0.61 mg Se/kg bw per day) or sodium selenite as a positive control at 0.8 mg/kg bw per day (corresponding to 0.35 mg Se/kg bw per day). The authors identified a no observed adverse effect level (NOAEL) of 114 mg Sel-Plex[®]/kg bw per day, equivalent to 0.23 mg Se/kg bw per day. However, in the view of the FEEDAP Panel, a NOAEL cannot be established since a dose-related effect was seen on the reduction of thymus weight and body weight for both sexes, and on the increase of plasma bilirubin in female rats. The same effects were seen in the sodium selenite group at comparable selenium exposure.

For the study with Beagle dogs (4 males and 4 females per group), Sel-Plex[®] was administered by gavage at doses corresponding to 0, 30, 100 and 300 mg Sel-Plex[®]/kg bw per day (equivalent to 0, 0.06, 0.2 and 0.6 mg Se/kg bw per day) or sodium selenite at 1.3 mg/kg bw per day (corresponding to 0.6 mg Se/kg bw per day). The identified NOAEL was 30.0 mg Sel-Plex[®]/kg bw per day, equivalent to 0.06 mg Se/kg bw/day²⁴; this is also consistent with the conclusions of Griffiths et al. (2006b). The NOAEL is based on the absence of increased plasma cholesterol (seen at higher doses). At the highest tested dose (300 mg Sel-Plex[®]/kg per day), thymus weight was reduced together with an increased thymic lymphoid depletion. Sodium selenite induced effects comparable to the high dose of Sel-Plex[®] (0.6 mg Se/kg bw per day).

Therefore, the two studies indicate that Sel-Plex[®] did not exert toxicological effects other than those provoked by sodium selenite. It is concluded that the toxic potential of Sel-Plex[®] is only related to its selenium content, no interactions between selenium and the other constituents of the yeasts are to be expected.

3.2.3. Safety for the target species

The FEEDAP Panel assessed in its opinion from 2006 two studies with chickens for fattening, one with laying hens, one with piglets, and three studies with ruminants. In its opinion from 2011, a tolerance study in lambs was assessed. All these studies confirmed the safety of the maximum authorised selenium content in feed (0.5 mg/kg) for the animal species/categories tested. Approximately the 10-fold of the authorised level was tolerated. The Panel therefore concluded that Sel-Plex[®] is a safe source of selenium in animal nutrition, provided that the legal provisions maximum dietary level of selenium in feed are respected. Following the requirements of the Guidance for renewal of authorisation of feed additives (EFSA FEEDAP Panel, 2013), the applicant summarised the current knowledge concerning the safety of the additive for the target species and reported various publications from which only two can be used in the context of this assessment.¹⁰ The FEEDAP Panel had already assessed one of the studies in a previous Sel-Plex[®] application concluding that lambs tolerated the additive at 10-fold (i.e. 5 mg Se from Sel-Plex[®]/kg milk replacer or pelleted complete diet) the authorised total selenium levels in feed (Juniper et al., 2009); the other paper dealt with the same subject in a variety of ruminants (dairy cows, beef cattle, calves and lambs) and also

²³ Technical Dossier (FAD-2005-0007)/Section IV/Annex 4.2.10.

²⁴ Technical Dossier (FAD-2005-0007)/Section IV/Annex 4.2.13.

identified that diets supplemented with Sel-Plex[®] containing up to 6.63 mg Se/kg DM were tolerated (Juniper et al., 2008).

The FEEDAP Panel confirms its former conclusion that Sel-Plex[®] is a safe source of selenium for all animal species.

3.2.4. Safety for the consumer

Selenium is the relevant component from Sel-Plex[®] as regards consumer safety. The UL for selenium has been set by the Scientific Committee on Food (European Commission, 2000) as 300 µg/day and 60 µg/day for adults and toddlers, respectively. Although several uncertainties still exist concerning the mechanisms and dose response of selenium toxicity, no new data have become known that could modify the current UL (EFSA NDA Panel, 2014). In the meanwhile, even though with large regional variations and uncertainties, available dietary surveys do not indicate a significant risk of selenium deficiency or of selenium excess in the EU population (EFSA NDA Panel, 2014).

The applicant submitted a series of documents, mainly previous EFSA opinions on selenised yeast-based additives, concerning the deposition in edible tissues and products of selenium from organic sources and the dietary exposure to selenium in Europe.¹⁰ The documents provided were already known to EFSA and confirm the previous assessment by the FEEDAP Panel that the use of selenised yeasts as a selenium source in animal nutrition leads to an enhanced deposition of in edible tissues and products, as compared to inorganic selenium sources at comparable concentrations in feeds; this is due to both increased oral absorption and increased uptake, e.g. through incorporation in body proteins, by tissues and products, including meat, eggs and milk. Consequently, the use of Sel-Plex[®] leads to a higher exposure of consumer to selenium in comparison to inorganic selenium sources, and therefore, the FEEDAP Panel reiterates its previous conclusion that a supplementation level of 0.2 mg Se from selenised yeasts/kg should not be exceeded, respecting the maximum total selenium content of 0.5 mg/kg complete feed, to ensure consumer safety.

A preliminary report on a meta-analysis on the correlation of selenium concentrations in feed and animal tissues/products was provided by the applicant.²⁵ This report intended to provide a more reliable basis to predict selenium concentration in animal tissues/products from the feed dietary selenium levels. However, the database is unclear, the time in which data have been collected is not given, an arbitrary differentiation is made from different meat sources and the selenium amounts reported were taken as added selenium in either form (organic or inorganic) to the endogenous selenium present in the feed. The author of the report concluded that overall the results of meta-analysis were very similar to those used in the 2011 EFSA FEEDAP report given the uncertainties associated with the data. In the view of the FEEDAP Panel, this preliminary report cannot be used to revise the previous proposal of limiting the maximum selenium supplementation from organic sources to 0.2 mg Se/kg feed.

3.2.4.1. Conclusions on safety for the consumer

No new evidence on consumer safety has been provided that would make the FEEDAP Panel reconsider its previous conclusion. Thus, the Panel confirms that the use of Sel-Plex[®] in animal nutrition does not pose a risk to consumers provided that the maximum selenium supplementation of 0.2 mg/kg feed from Sel-Plex[®] is not exceeded, yet respecting the maximum total selenium in feed of 0.5 mg/kg.

3.2.5. Safety for the user

3.2.5.1. Effects on the respiratory system

In the previous assessment, the FEEDAP Panel concluded that 'the use of Sel-Plex[®] is unlikely to elicit a significant exposure to selenium for the user. However, appropriate measures to minimize inhalation exposure to breathable selenium and protein components should be taken' (EFSA, 2006).

The highest dusting potential of the additive was 4.785 g/m³; the respirable and the thoracic fractions amounted up to 3.6% and 36.2%, respectively (see Section 3.1.3). Considering that the selenium concentration in the dust would correspond to that in the additive (2,143–2,433 mg Se/kg), it can be calculated that a maximum concentration of 11.6 mg Se/m³ could be released by the dust when handling the additive. Since no figure on the particle size distribution in dust was reported, the FEEDAP Panel, based on a conservative approach, estimated that respirable selenium from dust would

²⁵ Technical Dossier/Section III/Annex III_1_3.

be about 1.2 mg/m³, assuming that the dust consists only of particles ≤ 50 µm and its respirable fraction about 10% (3.6 of 36.2).

Concerning threshold limit values (TLV) for selenium compounds, maximum tolerable air concentrations between 0.02 and 0.2 mg Se/m³ have been set by different organisations (e.g. Deutsche Forschungsgemeinschaft (DFG) Maximale Arbeitsplatz Konzentration (MAK) List, Occupational Safety and Health Administration (OSHA)-Permissible Exposure Limit (PEL), and National European Authorities). Consequently, and considering the above estimate of selenium from the dust of the additive, its handling represents a risk to users by inhalation.

Owing to the proteinaceous nature of the additive, it should be considered a potential respiratory sensitiser.

3.2.5.2. Effects on eyes and skin

Eyes²⁶ and skin²⁷ irritation were evaluated in rabbits under 405 and 404 OECD Guidelines for Testing of Chemicals, respectively. According to the assessment criteria on the Regulation (EC) No 1272/2008²⁸, Sel-Plex[®] is considered as non-irritant to skin and eyes.

3.2.5.3. Conclusions on safety for the user

The additive is hazardous upon inhalation and a likely respiratory sensitiser. Owing to the high dusting potential, persons handling the additive are at risk by inhalation. It is considered not irritant to the eyes and skin.

3.2.6. Safety for the environment

In the previous opinion, the FEEDAP Panel concluded that 'As Sel-Plex[®] will replace other selenium sources, its use will not alter the concentration and distribution of selenium in the environment' (EFSA, 2006). Following the requirements of the Guidance for renewal of authorisation of feed additives (EFSA FEEDAP Panel, 2013), the applicant summarised the current knowledge concerning the safety of the additive for the environment and reported several publications from the EFSA-FEEDAP Panel, including those on Sel-Plex[®] (EFSA, 2006; EFSA FEEDAP Panel, 2011).¹⁰ Thus, there is no new evidence that could modify the Panel previous conclusion. Therefore, the FEEDAP Panel reiterates that the use of Sel-Plex[®] in feed does not pose an additional risk to the environment as long as the maximum authorised content in complete feed is not exceeded.

3.3. Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation²⁹ and Good Manufacturing Practice.

4. Conclusions

The applicant has provided evidence that the additive currently in the market complies with the conditions of authorisation.

The FEEDAP Panel confirms that Sel-Plex[®] is a safe dietary source of selenium for all animal species.

The FEEDAP Panel confirms that the use of Sel-Plex[®] in animal nutrition does not pose a risk to consumers provided that the maximum selenium supplementation of 0.2 mg/kg feed from Sel-Plex[®] is not exceeded, yet respecting the maximum total selenium in feed of 0.5 mg/kg.

The additive is hazardous upon inhalation and a likely respiratory sensitiser. It is considered not irritant to the eyes and skin.

The FEEDAP Panel reiterates that the use of Sel-Plex[®] in feed does not pose an additional risk to the environment as long as the maximum authorised content in complete feed is not exceeded.

²⁶ Technical Dossier/Supplementary Information (November 2016)/Annex 5.

²⁷ Technical Dossier/Supplementary Information (November 2016)/Annexes 3 and 4.

²⁸ Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1.

²⁹ Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.

5. Recommendations

In accordance with the more recent relevant opinions on selenium from selenised yeasts, the FEEDAP Panel recommends the denomination of the additive under assessment as 'Selenium in the form of organic compounds produced by the selenium enriched yeast *Saccharomyces cerevisiae* CNCM I-3060 (Selenised yeast inactivated)'.

Documentation provided to EFSA

- 1) SEL-PLEX[®] Organic form of Selenium produced by *Saccharomyces cerevisiae* CNCM I-3060 (Selenised yeast inactivated). December 2015. Submitted by Alltech Ireland.
- 2) SEL-PLEX[®] Organic form of Selenium produced by *Saccharomyces cerevisiae* CNCM I-3060 (Selenised yeast inactivated). Supplementary information. November 2016. Submitted by Alltech Ireland.
- 3) SEL-PLEX[®] Organic form of Selenium produced by *Saccharomyces cerevisiae* CNCM I-3060 (Selenised yeast inactivated). Supplementary information. December 2016. Submitted by Alltech Ireland.
- 4) SEL-PLEX[®] Organic form of Selenium produced by *Saccharomyces cerevisiae* CNCM I-3060 (Selenised yeast inactivated). Supplementary information. February 2017. Submitted by Alltech Ireland.
- 5) Comments from Member States.

Chronology

Date	Event
17/12/2015	Dossier received by EFSA
19/1/2016	Reception mandate from the European Commission
11/4/2016	Application validated by EFSA – Start of the scientific assessment
11/7/2016	Comments received from Member States
22/7/2016	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: Characterisation and safety</i>
7/11/2016	Reception of supplementary information from the applicant - Scientific assessment re-started
10/11/2016	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended <i>Issues: Characterisation</i>
12/12/2016	Reception of supplementary information from the applicant - Scientific assessment re-started
20/11/2017	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended <i>Issues: Characterisation</i>
9/2/2017	Reception of supplementary information from the applicant - Scientific assessment re-started
5/7/2018	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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Abbreviations

ADME	absorption, distribution, metabolism and excretion
bw	body weight
cfu	colony forming unit
CNCM	Collection Nationale de Cultures de Microorganismes
DFG	Deutsche Forschungsgemeinschaft
EMA	European Medicines Agency
EURL	European Union Reference Laboratory
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
ICP-MS	inductively coupled plasma mass spectrometry
LOD	limit of detection
LOQ	limit of quantification
MAK	Maximale Arbeitsplatz Konzentration
NOAEL	no observed adverse effect level
OSHA	Occupational Safety and Health Administration
PCB	polychlorinated biphenyl
PCDD-F	polychlorinated dibenzo- <i>p</i> -dioxin/dibenzofuran
PEL	Permissible Exposure Limit
QPS	Qualified Presumption of Safety
SeCys	selenocysteine
SeMet	selenomethionine
Sepp1	selenoprotein P
TEQ	toxic equivalents
TLV	threshold limit values
WHO	World Health Organization

Annex A – Selenium speciation of SEL-PLEX[®] aqueous fraction

Selecompound	Concentration (%)
Methyl dehydrohomocysteine	0.6
Selenohomolanthionine	
Selenohomolanthionine	
Selenohomocysteine-ribofuranose	
γ -Glutamoylselenocystathione	0.2
2,3-DHP-selenolanthionine	0.2
γ -Glutamoyl-methyl selenocysteine	0.7
2,3-DHP-selenocystathionine	
Selenogluthathione-cysteine	0.4
Glutathione-selenocysteinylglycine	0.1
Selenogluthathione-selenocysteine	0.1
Methylselenogluthathione	
2,3-DHP-selenocysteine-cysteine	
<i>N</i> -acetylcysteine-selenogluthathione	
<i>N</i> -acetylcysteine-selenogluthathione	0.2
Glutathione-selenohomocysteine	
2,3-DHP-selenocysteine-cysteinylglycine	0.3
2,3-DHP-selenohomocysteine-cysteinylglycine	
2,3-DHP-selenocysteine-selenocysteine	0.2
Selenogluthathione	
2,3-DHP-selenocysteine-selenohomocysteine	
<i>N</i> -acetylcysteine-selenohomocysteine	0.1
γ -Glutamoyl selenocysteine- γ -glutamoyl cysteine	0.7
Glutathione- γ -glutamoylselenocysteine	0.5
Methylthioselenogluthathione	
Di- γ -glutamoylselenocysteine	
<i>N</i> -acetylselenocysteine-selenohomocysteine	1.2
Selenogluthathione-glutathione	
Selenogluthathione- γ -glutamoylselenocysteine	
Di-selenogluthathione	0.2
Selenomethyl-selenogluthathione	
<i>N</i> -acetylcysteine-selenogluthathione	0.2
Selenodiglutathione	
2,3-DHP-selenocysteine-gama-glutamoylcysteine	1.7
Thio-diselenogluthathione	
Glutathione-2,3-DHP-selenocysteine	
Glutathione-2,3-DHP-selenohomocysteine	
Glutathione- <i>N</i> -acetylselenohomocysteine	
γ -Glutamoylcysteine-2,3-DHP-selenocysteine	
Selenogluthathione-2,3-DHP-selenocysteine	0.6
Selenogluthathione-2,3-DHP-selenohomocysteine	
Ethyl selenoadenosine	0.1
Seleno(hydroxy)-selenophene-[3'-deoxy-adenosine]	0.1
Seleno-adenosyl-Se(methyl)-selenoxide	1.1
2,3-DHP-selenocysteine-cysteinyl glycine	0.1
<i>N</i> -acetylcysteine-selenohomocysteine	0.3
Methylthio-selenogluthathione	
Allylselenoadenosyl homocysteine	

Selecompound	Concentration (%)
Seleno-hydroxy adenosyl homocysteine	0.9
Seleno-adenosyl-Se(methyl)-selenoxide	
Adenosyl-hydroxy selenoxide	
Seleno-adenosyl homocysteine	
Seleno adenosine	
Seleno(hydroxy)-selenophene-[3'-deoxy-adenosine]	
No quantified (LOD=2ppb) and Unidentified	3.7

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