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Assessment of the application for renewal of authorisation of selenomethionine produced by *Saccharomyces cerevisiae* NCYC R397 for all animal species

EFSA Panel on Additives and Products or Substances used in Animal Feed (EFSA FEEDAP Panel), Vasileios Bampidis, Giovanna Azimonti, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Maryline Kouba, Mojca Kos Durjava, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa, Ruud Woutersen, Gerhard Flachowsky, Jürgen Gropp, Francesco Cubadda, Gloria López-Gálvez and Alberto Mantovani

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* NCYC R397 (Alkosel®) for all animal species. The FEEDAP Panel has delivered two opinions (on 2007 and 2016) on the safety and efficacy of the additive. The additive is characterised as organic selenium mainly selenomethionine (63%); it was initially authorised in 2007 with a content of 2,000–2,400 mg Se/kg (97–99 % of organic selenium) and in 2017 the authorisation was further amended to introduce a selenium range of 2,000–3,500 mg Se/kg. Additionally, in 2013, the initial authorising Regulation was modified to introduce a maximum supplementation selenium from this additive in feed (0.2 mg Se from Alkosel®/kg feed). 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 Alkosel® in animal nutrition does not pose a risk to consumers provided that the maximum selenium supplementation of 0.2 mg/kg feed from Alkosel® is not exceeded, yet respecting the maximum total selenium in feed of 0.5 mg/kg. Data on the characterisation of the additive and studies on skin/eyes effects led the Panel reconsider the safety for the user, concluding that Alkosel® is (i) hazardous upon inhalation, (ii) non-irritant to skin and considered irritant for the eyes and mucosae, and (iii) a dermal sensitiser and likely a respiratory sensitiser. A recommendation regarding the denomination of the additive under assessment was proposed by the Panel.

Keywords: nutritional additive, compounds of trace elements, selenium, selenised yeast, *Saccharomyces cerevisiae* NCYC R397, ALKOSEL®, safety

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Correspondence: feedap@efsa.europa.eu

Panel members: Giovanna Azimonti, Vasileios Bampidis, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Maryline Kouba, Mojca Kos Durjava, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa and Ruud Woutersen.

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 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 Lallemand SAS[2] for renewal of the authorisation of selenomethionine produced by *Saccharomyces cerevisiae* NCYC R397, 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 24 August 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 on the efficacy of the product organic form of selenium produced by *Saccharomyces cerevisiae* NCYC R397, when used under the proposed conditions of use (see Section 3.1.4).

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 this additive (EFSA, 2007a; EFSA FEEDAP Panel, 2016).

Selenomethionine (organic form of selenium produced by *S. cerevisiae* NCYC R397) is authorised for all animal species;[3,4,5] the maximum selenium supplementation rate with this additive is of 0.2 mg Se from Alkosel®/kg complete feed.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[6] in support of the authorisation request for the use of selenomethionine produced by *S. cerevisiae* NCYC R397 for all animal species. The technical dossier was prepared following the provisions of Article 14 of Regulation (EC) No 1831/2003, Regulation (EC) No 429/2008[7] 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] Lallemand SAS, 19 Rue des Briquetiers, BP 31702, Blagnac. France.
[3] Commission Regulation (EC) No 634/2007 of 7 June 2007 concerning the authorisation of selenomethionine produced by *Saccharomyces cerevisiae* NCYC R397 as a feed additive. OJ L 146, 8.6.2007, p. 14.
[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] Commission Implementing Regulation (EU) 2017/1086 of 19 June 2017 amending Regulation (EC) No 634/2007 as regards the characterisation of selenomethionine produced by *Saccharomyces cerevisiae* NCYC R397.
[6] FEED dossier reference: FAD-2016-0039.
[7] 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 and 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.[8]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of selenomethionine produced by *S. cerevisiae* NCYC R397 for all animal species is in line with the principles laid down in Regulation (EC) No 429/2008 and the 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 product selenomethionine produced by *S. cerevisiae* NCYC R397 (selenised yeast inactivated) as a nutritional additive (functional group: compounds of trace elements) for all animal species. The additive is characterised as organic selenium mainly selenomethionine (63 %); it was initially authorised with a content of 2,000–2,400 mg Se/kg (97 to 99 % of organic selenium). The authorisation was further amended to introduce a selenium range of 2,000–3,500 mg Se/kg.[5]

The maximum selenium supplementation rate with this additive is of 0.2 mg Se from Alkosel®/kg complete feed.

3.1. Characterisation

3.1.1. Characterisation of the additive

Analytical data on the composition of the additive were provided for three batches.[9] On average, total selenium (Se) content was 2,171 mg Se/kg additive (range 2,070–2,337), selenium from selenomethionine (SeMet) 1554 mg Se/kg (range 1,341–1,697), corresponding to 71.5% of the total selenium content (specification 63%). Levels of protein (average 52.9%) and of moisture (average 2.2%) are also in agreement with the specification: ≥ 40% and < 7%, respectively.

The applicant submitted two reports on the speciation of selenium from the selenised yeast product: one report, based on the analysis of one batch, corresponded to the Alkosel® containing 2,000–2,400 mg total Se/kg[10] and another one based on five batches corresponded to Alkosel-3000 product (containing a minimum of 3,000 mg total Se/kg).[11] From these analyses, it could be confirmed that the product contains a maximum 2% of inorganic selenium. Additionally, the applicant submitted data of the levels of SeMet and selenocysteine (SeCys) in two batches of the additive[12] being the values rather variable: 59.3 and 81.0% for SeMet, and 17.4 and 25.9% for SeCys; the applicant regarded the variability of the analytical results to the manufacturing process and analytical issues.

The following impurities are controlled as part of the HACCP related to the manufacture of Alkosel® and were analysed in three batches (range of results in parenthesis):

- Microbiological contaminations: total plate count (100–200 colony forming units (CFU)/g), yeast and moulds (< 10 CFU/g), coliforms (< 10 CFU/g), *Escherichia coli* (< 10 CFU/g), *Staphylococcus aureus* (negative coag+/g) *Salmonella* (negative in 25 g).[13]
- Mycotoxins: aflatoxins B1 (< 1 μg/kg), B2 (< 1 μg/kg), G1 (< 1 μg/kg) and G2 (< 1 μg/kg).[14]
- Heavy metals (lead < 0.01 mg/kg, cadmium 0.01–0.02 mg/kg and mercury < 0.05 mg/kg) and arsenic (< 0.05 mg/kg).

[8] The report linked to the previous dossier (related to EFSA-Q-2005-117) is available on the EURL website: https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2005-0012.pdf
[9] Technical Dossier/Section II/Annex II 3a.
[10] Technical Dossier/Section II/Annex II 3k.
[11] Technical Dossier/Section II/Annex II 3l.
[12] Technical Dossier/Section II/Section 2.1.3.3.
[13] Technical Dossier/Section II/Annex_II_3a.
[14] Technical Dossier/Section II/Annex_II_4a.

- Dioxins and dioxin-like polychlorinated biphenyls (PCBs): 0.061–0.073 ng WHO-PCDD/F-TEQ and 0.037–0.041 ng WHO-PCB-TEQ, respectively.[14]

All the reported values are within limits set in the Directive 2002/32/EC on undesirable substances in animal feed[15] for feed additives belonging to the functional group compounds of trace elements or, where no specific limit is mentioned, do not represent a safety concern.

3.1.2. Characterisation of the production strain

The additive is produced by a strain of *Saccharomyces cerevisiae*, deposited in the 'National Collection of Yeast Cultures (NCYC)' of the UK with deposition number NCYC R397.[16] [redacted]

3.1.3. Physical characteristics of the product

Alkosel® is a light brown tan free-flowing powder with a typical baker's yeast smell. The FEEDAP Panel notes that in the previous application of 2006 the applicant indicated that the product is granulated.

Particle size distribution determined by mechanical sieving in three batches was provided, although no information on distribution of particles under 45 μm was given. Following the FEEDAP Panel request of supplementary information on particle size distribution and dusting potential of the additive Alkosel®, the applicant submitted data from spray dried batches, [redacted] Results of the particle size distribution of the additive measured by laser diffraction in three batches ranged from 5.0 to 7.9 % for particles < 10 μm, from 34.5 to 43.1 % for particles < 50 μm, and from 69.2 to 76.9 % for particles < 100 μm.[20] The dusting potential of Alkosel® determined by the Stauber–Heubach method was on average 0.96 g/m^3 (0.665 to 1.46 g/m^3).

3.1.4. Manufacturing process

The manufacturing process is fully described in the technical dossier. [redacted]

3.1.5. Stability and homogeneity

No new data have been provided on shelf-life of the additive.[25] Since only minor changes have been introduced, it can be reasonably assumed that shelf-life of the additive would remain unchanged: 2 months under standard (25°C/60% relative humidity (RH)) or accelerated 40°C/75 % RH) storage conditions.

[15] Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed.
[16] Technical Dossier/Section II/Annex_II_6b. Technical Dossier/Supplementary Information/Annex 4.
[redacted]
[20] Technical Dossier/Supplementary Information/Annex2c.
[redacted]
[25] Technical Dossier/Section II/Annex_II_8b, Annex_II_8c.

The applicant provided data on the stability of the additive in two commercial vitamin/mineral premixtures (one containing Alkosel® and sodium selenite and the other containing only Alkosel®).[23] Since only total selenium was analysed, data on the premixture containing Alkosel® and sodium selenite cannot be considered. For the premixture supplemented with Alkosel® as a single source of selenium, 6- and 9-month stability data do not indicate a loss of total selenium during storage; however, initial data were only provided as calculated. No data on stability of SeMet were provided.

No new homogeneity data have been provided. The capacity of the additive to be homogeneously distributed in premixtures and feedingstuffs was previously demonstrated (EFSA, 2007a).

3.1.6. Conditions of use

The additive is intended to be used for all animal species/categories up to a total of 0.2 mg Se/kg complete feeds (12 % moisture), being the maximum authorised total selenium content in complete feed of 0.5 mg/kg. The additive is to be incorporated into feed in the form of a premixture. These terms are in agreement with the provisions of the Regulation authorising the additive.

The conditions of use include provisions 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, having being established the identity of the strain (see Section 3.1.2), *S. cerevisiae* NCYC R397 is considered by EFSA to be suitable for the Qualified Presumption of Safety (QPS) approach to safety assessment (EFSA, 2007b; 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 evidence aiming to support 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. The applicant submitted the respective report.[26]

The applicant submitted the result of a literature search, which covered the period from December 2006 until January 2017, to provide information on the safety of the feed additive under the conditions of authorisation. The following channels were searched: Discovery tools, 'Science portals' and Bibliography databases (Scopus, Agris and CAB Abstract). Two strategies as key-words/search terms were applied: one with 'NCYC R397', 'alkosel' and 'lalmin selenium' (name of Akosel® in human nutrition), and another with extended (generic) terms such as '*Saccharomyces cerevisiae*', 'selenised yeast' and 'selenomethionine'; however, the applicant stated that latter strategy led to papers in which selenised yeasts from other companies were tested and therefore only the former strategy was considered. Only published work after 2006 was retained. The applicant identified a total of 33 relevant studies (see Appendix A); most of them refer to experiments performed in target species. Those considered relevant by the Panel are mentioned in the respective section.

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

In its opinion of 2006, the FEEDAP Panel concluded that 'Several studies in dairy cows indicated that Alkosel® supplementation increased the levels of Se in whole blood, plasma and blood GSH-Px activity, demonstrating the bioavailability of Se from Se-enriched yeast in lactating cows. Based on the extensive knowledge of Se metabolism, the FEEDAP Panel considers these studies as a reasonable demonstration of bioavailability for all animal species' (EFSA, 2007a).

From the literature search provided by the applicant (see above under Section 3.2. Safety) some studies identified are relevant to the ADME of Alkosel®: namely, one study in laying hens and its effects on performance, eggshell quality and tissue selenium distribution (Invernizzi et al., 2013) and another in camels (Faye et al., 2014). These studies confirm SeMet is more easily absorbed, metabolised and retained in tissues than sodium selenite.

A further paper was identified by the FEEDAP Panel. Burk and Hill (2015) reviewed and discussed the recent knowledge on SeMet metabolism, pointing to the role of selenoprotein P (Sepp1), which is synthesised by 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

[26] Technical Dossier/Supplementary Information/Annex SafetyReview.

apoER2 and megalin. Expression of the apoER2 gene determines the selenium uptake by most tissues; megalin mediates selenium uptake by kidney cells. One main metabolite, selenosugar (1β-methylseleno-*N*-acetyl-D-galactosamine) seems to act as a selenium reservoir in tissues.

The FEEDAP Panel concludes that the new scientific evidence lends further support to the previous ADME assessment of SeMet.

3.2.2. Toxicological studies

The toxicology of selenium has been recently reviewed by the European Medicines Agency (EMA, 2015), as well as by Alexander et al. (2015). No new findings were reported on the referred documents that allow to modify the previous EFSA opinion of Alkosel® toxicological conclusions (EFSA, 2007a). Thus, the FEEDAP panel reiterates that selenium supplementation using the additive Alkosel® does not introduce any different toxicological concerns compared to other sources of selenium.

3.2.3. Safety for the target species

In its first opinion on Alkosel (EFSA, 2007a), the FEEDAP Panel concluded that Se from Alkosel® at the maximum permitted level (0.5 mg/kg complete feed) is safe for all animal species.

From the literature search provided by the applicant (see above under Section 3.2. Safety), 16 studies were identified as containing data supporting the safety of the additive for the target species. The main objective of several of these studies was not to test the safety of the additive for the target species, but selenium deposition in tissues and products or efficacy related to different endpoints; relevant studies and results are further described in the section on safety for the consumer (Section 3.2.4.1).

In 10 of the 16 studies, only levels exceeding the maximum content for supplemental selenium were tested; these are consequently not further considered in this section. The remaining six studies (three on laying hen and one each on ducks, partridges and dairy cows) are described below.

In three studies on 22-week old laying hens, in which diets supplemented by 0.4 and 0.5 mg Se from Alkosel®/kg were fed for 8 weeks, no adverse effects were reported (Buckiuniene et al., 2013; Invernizzi et al., 2013; Buckiūnienė et al., 2016).

Ding et al. (2016) assessed the requirements of red-legged partridges (*Alectoris rufa*) for selenium by feeding graded levels of 0.2, 0.3, 0.4 and 0.5 mg Se from Alkosel®/kg. Selenium supplementation above 0.2 mg/kg, and up to 0.4 mg/kg, improved laying rate and hatching rate. No adverse effects related to the use of Alkosel® were reported.

Ducks fed from hatch for 49 days a diet supplemented with 0.4 mg Se from Alkosel®/kg had a significantly higher live weight compared to the unsupplemented control group, but also compared to 0.6 mg supplemental selenium from Alkosel®/kg (Baltić et al., 2015). The relative weight gain depression was caused in the view of the authors by a reduced feed intake.

Grilli et al. (2013) fed dairy cows diets supplemented with selenium from Alkosel® (and microencapsulated sodium selenite) up to 0.5 mg Se/kg for eight weeks. No adverse effect of Alkosel® was reported.

The majority of these studies dealt with selenium concentrations from Alkosel® slightly above the EU threshold for total selenium. The FEEDAP Panel notes that no concerns existed on the safety of selenium from Alkosel® at the maximum authorised content of 0.5 mg/kg complete diet when Alkosel® was initially assessed by EFSA (EFSA, 2007a); this statement is also currently valid.

There are two thresholds for selenium in feed, one for total selenium (maximum 0.5 mg/kg complete feed) and another for supplemental selenium from selenised yeasts (maximum 0.2 mg/kg complete feed). The restriction for supplemental selenium is not related to any aspect of target animal safety; it has been set for consumer safety reasons only.

The review of the above-mentioned studies did not provide any new information that would require modification of the previous EFSA conclusions on the safety of this additive for the target animals. Therefore, the FEEDAP Panel concludes that the use of selenised yeast from *S. cerevisiae* NCYC R397 under the authorised conditions of use is safe for the target species.

3.2.4. Safety for the consumer

Selenium is a trace essential element that at excessive intakes has a recognised toxicity in mammals including humans. The UL for selenium has been set by the Scientific Committee on Food (EC, 2000) (adults: 300 μg/day; toddlers: 60 μg/day), and used by the FEEDAP Panel in previous

assessments of the consumer safety for different selenium compounds. To the best knowledge of FEEDAP Panel, there are no new data that can modify the UL set in 2000, as confirmed also by a more recent opinion of EFSA NDA Panel on Dietary Reference Values for selenium (EFSA NDA Panel, 2014).

EFSA considered that a 0.2 mg/kg feed selenium supplementation with selenised yeasts (within the maximum limit of total 0.5 mg Se/kg feed) was safe for the consumer (EFSA FEEDAP Panel, 2011); this assessment was based on the higher deposition of selenium in tissues when a organic selenium is used as source of selenium supplementation.

From the literature search provided by the applicant (see above under Section 3.2 Safety), studies relevant to selenium deposition in edible tissues and products and the associated consumer exposure were identified. The FEEDAP Panel considered the studies that investigated tissue deposition and did use SeMet supplementation of feedingstuffs at levels compatible with the maximum authorised selenium levels in the EU. Eight relevant studies were identified: two on dairy cows, five on laying hens, one on ducks and one in pheasants; some of these studies are also reported above, under safety for the target animals (see Section 3.2.3).

3.2.4.1. Studies on tissue deposition

3.2.4.1.1. Dairy cows

Dairy cows were fed during 56 days with sodium selenite (0.3 mg Se/kg feed), microencapsulated sodium selenite (0.3 or 0.5 mg Se/kg feed) and Alkosel® (0.3 or 0.5 mg Se/kg feed). Cows supplemented with either microencapsulated selenium or with Alkosel® had higher milk selenium concentration compared to non-microencapsulated sodium selenite. In particular, with regard to the comparison between conventional sodium selenite and Alkosel®, mean levels in milk of cows treated with sodium selenite (19.05 μg/kg) were significantly lower compared to those supplemented with either 0.3 mg/kg (23.27 μg/kg) or 0.5 mg/kg (26.70 μg/kg) of selenium from Alkosel® (Grilli et al., 2013).

Ten mid-lactation Estonian Red dairy cows were supplemented for 64 days with inorganic selenium (0.39 mg kg/feed from sodium selenite) followed by a 57-day period of supplementation with organic and inorganic selenium (0.44 mg Se kg/feed, provided 50% from sodium selenite and 50% from Alkosel®). The 50% supplementation with organic selenium increased the selenium content in blood (from 186.5 to 287.9 μg/kg) and especially in milk (from 17.1 to 51.8 μg/kg) and, consequently, in the Edam-type cheese made therefrom (from 146 to 361 μg/kg) (Ling et al., 2017).

3.2.4.1.2. Laying hens

Cattaneo et al. (2008) investigated the effect of selenium overdose (supplemental 0.4 vs. 5 mg Se/kg) from selenite and from two Se-enriched yeasts (organic selenium species not mentioned and contents of organic forms not given) in 22-week-old laying hens for 8 weeks. Hens supplemented with 0.4 mg Se from Se-enriched yeast/kg feed had a significantly higher mean selenium content in eggs (0.33–0.37 mg/kg) than the group supplemented with sodium selenite (0.21 mg/kg).

In a 6-week study on different selenium sources, Chinrasri et al. (2009) compared two groups of hens fed selenium from sodium selenite or Alkosel® (0.3 mg/kg feed each). Hens supplemented with Alkosel® had significantly higher mean selenium content in eggs (3.28 mg/kg dry matter (DM) vs. 2.28 mg/kg DM in the sodium selenite group). Whereas the selenium levels in yolk were comparable between the two groups, the selenium increase in the whole eggs of the Alkosel® supplemented group was due to a nearly 3-fold selenium increase in the albumen.

Fanelli (2011) compared the selenium levels in eggs, breast muscle, liver, kidney and skin following the supplementation of laying hens feed with sodium selenite or Alkosel® (both at 0.4 mg Se/kg feed) during eight weeks. Selenium deposition was markedly and significantly increased in breast muscle in the Alkosel®-treated group as compared with sodium selenite (1.22 vs. 0.39 mg/kg); similarly, statistically significant increases were also observed from the Alkosel®-treated group in selenium in eggs (1.4 vs. 0.9 mg/kg); numerical increases were measured in liver (1.84 vs 1.69 mg/kg) and skin (0.40 vs. 0.31 mg/kg). The selenium deposition in kidney was slightly but significantly increased in the sodium selenite group compared with the Alkosel® group (1.45 vs. 1.31).

Buckiuniene et al. (2013) compared the influence of 0.5 mg supplemental selenium from sodium selenite and Alkosel® in the diet of 22-week-old laying hens on yolk selenium and other egg compositional parameters (cholesterol, fatty acid profile and malondialdehydes) for 8 weeks. Selenium in egg yolk was slightly, albeit statistically significant, lower in the Alkosel® group compared to sodium selenite group (1.0 vs. 1.3 mg/kg egg yolk, respectively). The data appear to confirm that yolk is not

the target of the enhanced deposition of selenium from Alkosel in eggs (see above, Chinrasri et al., 2009).

Invernizzi et al. (2013) evaluated the effects on performance, eggshell quality, and tissue selenium distribution of 0.4 mg supplemental selenium from Alkosel®/kg feed in 22-week-old laying hens for 8 weeks. Control group was fed with 0.11 mg Se/kg feed. Breast muscle selenium content was significantly higher in animals fed with Alkosel® as compared with control or sodium selenite groups (1.22 vs. 0.42 and 0.39 μg/g, respectively). Liver, skin and kidney selenium levels were similar in sodium selenite (1.69, 0.31 and 1.45 μg/g, respectively) and in Alkosel® fed groups (1.84, 0.40, and 1.31 μg/g, respectively).

In a 12-week study on the effect of organic selenium supplementation on egg quality parameters, Zduńczyk et al. (2013) compared the effect of different supplementation levels of selenium from Alkosel® (0.15 and 0.30 mg Se/kg) on various parameters and quality of eggs. Consistently with other papers, slightly but significantly, higher selenium content in the yolk was observed only at the highest selenium supplementation level, 1.39 vs. 1.07 μg Se/g.

3.2.4.1.3. Ducks

Baltić et al. (2015) compared the effects on selenium deposition in liver and breast and thigh muscles of different levels of Alkosel® supplementation (equivalent to 0.2, 0.4 and 0.6 mg Se/kg feed) in 1-day-old ducks during 49 days; the background selenium content of feed was 0.04 mg/kg. Statistically significant and dose-related increases of selenium deposition were observed for all three tested tissues: liver (0.33, 0.56 and 0.93 mg/kg), breast muscle (0.27, 0.58 and 0.87 mg/kg) and thigh muscle (0.21, 0.42 and 0.64 mg/kg) when comparing the three supplementation levels of 0.2, 0.4 and 0.6 mg/kg, respectively.

3.2.4.1.4. Pheasants

Obradović et al. (2014) studied the effects of selenium from Alkosel® (0.3 or 0.4 mg Se) added to a diet (with 0.3 mg Se background level/kg) on 6-week old male and female pheasants, for 60 days. Animals fed diets with a total of 0.7 mg Se/kg had significantly higher selenium content in breast (0.14 mg/kg), thighs/drumsticks (0.11 mg/kg) and liver (0.41 mg/kg) compared to the control (breast 0.121 mg/kg; thighs/drumstick 0.102 mg/kg; liver 0.345 mg/kg) or the 0.6 mg Se/kg supplemented group (breast 0.129 mg/kg; thighs/drumstick 0.106 mg/kg; liver 0.383 mg/kg).

3.2.4.1.5. Conclusions on tissue deposition

The studies performed after 2006 led further support to the previous conclusions by the FEEDAP Panel that selenomethionine from selenised yeasts elicits a dose-related deposition of selenium in edible tissues and products. In addition, consistent scientific evidence, reviewed in this and in previous EFSA opinions support the fact that edible tissues and animal products – particularly meat, whole eggs and milk – from animals fed diets supplemented with selenium sources based on SeMet as the predominant selenocompound, contain significantly more selenium than those from animals given inorganic sources of selenium. The findings confirm that the increase of selenium deposition from SeMet-based sources, albeit of variable extent, generally occurs in the approximate twofold range.

3.2.4.2. Conclusions on consumer safety

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 Alkosel® in animal nutrition does not pose a risk to consumers provided that the maximum selenium supplementation of 0.2 mg/kg feed from Alkosel® is not exceeded, yet respecting the maximum total selenium in feed of 0.5 mg/kg.

3.2.5. Safety for the user

When first assessing Alkosel®, the FEEDAP Panel concluded that 'the use of Alkosel® is unlikely to elicit a significant exposure to Se for the user. However, appropriate measures to minimize skin contact and inhalation exposure to Alkosel® should be taken' (EFSA, 2007a).

From the literature search provided by the applicant (see above under Section 3.2 Safety), no studies relevant to safety for the user were identified.

3.2.5.1. Effects on the respiratory system

The highest dusting potential of the additive was 1.46 g/m^3. It is considered that the selenium concentration in dust would correspond to that in the additive (maximum analysed value: 2337 mg Se/kg). It can therefore be calculated that a maximum concentration of 3.4 mg Se/m^3 could be released by the dust when handling the additive. A conservative estimate of respirable selenium from dust would be about 0.6 mg/m^3.[27]

Concerning threshold limit values (TLV) for selenium compounds, maximum tolerable air concentrations between 0.02 and 0.2 mg Se/m^3 have been set by different organisations (e.g. German Maximale Arbeitsplatz Konzentration (MAK) List, Occupational Safety and Health Administration (OSHA), 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.

No data on respiratory sensitisation was made available in the dossier; taking into account the proteinaceous nature of the additive, the FEEDAP Panel considers it as a likely respiratory sensitiser.

3.2.5.2. Effects on eyes and skin

A study on dermal irritation/corrosion performed in rabbits under the OECD guideline 404 was provided; [redacted] the additive was considered as non-irritant for the skin. According to information provided in the Safety Data Sheet, the contact of the product with eyes causes possible redness and irritation;[29] therefore, the additive is considered irritant for the eyes and mucosae.

A skin sensitisation test was carried out according to the OECD guideline 429. [redacted] considered a dermal sensitiser, under the subcategory 1B ('may cause an allergic skin reaction').

3.2.5.3. Conclusions on safety for the user

Alkosel® is hazardous upon inhalation; persons handling the additive are at risk. The additive is non-irritant to skin and is considered irritant for the eyes and mucosae. The additive is a dermal sensitiser and likely a respiratory sensitiser.

3.2.6. Safety for the environment

In the previous opinion, the FEEDAP Panel concluded that 'The use of Alkosel® at recommended levels is unlikely to alter the concentration and distribution of selenium in the environment, as Alkosel® will replace other Se additives and does not present therefore an additional load to the environment' (EFSA, 2007a).

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 some publications from the EFSA FEEDAP Panel, including that on Alkosel® (EFSA, 2007a).[32] Thus, there is no new evidence that would lead to modify the Panel's previous conclusion. Therefore, the FEEDAP Panel reiterates that the use of Alkosel® in feed does not pose an additional risk to the environment as long as the maximum authorised content in complete feed is not exceeded.

[27] The respirable fraction in the additive was 7.9 %; the fraction < 50 μm was 43.1 %. Assuming that the dust consists only of particles ≤ 50 μm, its respirable fraction could be estimated to be 18.2 % (7.9 of 43.1). The selenium concentration in the respirable dust would then be 0.62 mg/m^3 (18.2 × 3.4 mg Se/m^3 per 100).

[29] Technical Dossier/Section II/Annex_II_9a.

[32] Technical Dossier/Section III. Technical Dossier/Supplementary Information/Annex SafetyReview.

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 Regulation[33] and Good Manufacturing Practice.

4. Conclusions

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

The FEEDAP Panel confirms that the use of Alkosel® under the current authorised conditions of use is safe for all animal species, the consumers and the environment.

The FEEDAP Panel concludes that Alkosel® is hazardous upon inhalation; persons handling the additive are at risk. The additive is non-irritant to skin and is considered irritant for the eyes and mucosae. The additive is a dermal sensitiser and likely a respiratory sensitiser.

5. Recommendation

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* NCYC R397 (Selenised yeast inactivated)'. In the view of the Panel, the denomination of selenised-yeast derived additives as *Selenomethionine* could be misleading.

Documentation provided to EFSA

1) ALKOSEL®R397 Selenomethionine produced by *Saccharomyces cerevisiae* NCYC R397 (Selenised yeast inactivated). June 2016. Submitted by Lallemand SAS.
2) ALKOSEL®R397 Selenomethionine produced by *Saccharomyces cerevisiae* NCYC R397 (Selenised yeast inactivated). Supplementary information. June 2017. Submitted by Lallemand SAS.
3) Comments from Member States.

Chronology

Date	Event
22/06/2016	Dossier received by EFSA
12/07/2016	Reception mandate from the European Commission
24/08/2016	Application validated by EFSA – Start of the scientific assessment
07/11/2016	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterisation and safety*
24/11/2016	Comments received from Member States
30/06/2017	Reception of supplementary information from the applicant - Scientific assessment re-started
28/11/2018	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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Abbreviations

ADME	absorption, distribution, metabolism and excretion
CFU	colony forming unit
DM	dry matter
EURL	European Union Reference Laboratory
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
HACCP	Hazard analysis and critical control points
MAK	Maximale Arbeitsplatz Konzentration
NCYC	National Collection of Yeast Cultures
OECD	Organisation for Economic Co-operation and Development
OSHA	Occupational Safety and Health Administration
PCB	polychlorinated biphenyl
PCDD/F	polychlorinated dibenzo-*p*-dioxin/dibenzofuran
QPS	Qualified Presumption of Safety
RH	relative humidity
SeCys	selenocysteine
SeMet	selenomethionine
Sepp1	selenoprotein P
TEQ	toxic equivalent
TLV	threshold limit value
WHO	World Health Organization

Appendix A – List of references retrieved from the literature search provided by the applicant to support safety of the additive

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