SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 25 October 2017

doi: 10.2903/j.efsa.2017.5060

Statement on the safety of synthetic L-ergothioneine as a novel food – supplementary dietary exposure and safety assessment for infants and young children, pregnant and breastfeeding women

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Dominique Turck, Jean-Louis Bresson, Barbara Burlingame, Tara Dean, Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Kristina Pentieva, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Daniel Tomé, Marco Vinceti, Peter Willatts, Karl-Heinz Engel, Rosangela Marchelli, Annette Pöting, Morten Poulsen, Josef Rudolf Schlatter, Reinhard Ackerl and Henk van Loveren

Abstract

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to provide a supplementary dietary exposure and safety assessment of synthetic L-ergothioneine for those groups of the population which had been excluded by the applicant in the original application, i.e. infants and young children (i.e. toddlers), pregnant and breastfeeding women. Thus, intake estimates were calculated for these population groups and the following maximum anticipated daily intakes of L-ergothioneine from the NF, in addition to the background diet, were calculated: 2.82 mg/kg body weight (bw) per day for infants, 3.39 mg/kg bw per day for toddlers and 1.31 mg/kg bw per day for adults including pregnant and breastfeeding women. The Panel considers that based on the overall toxicological data the no-observed-adverse-effect level (NOAEL) of 800 mg/kg bw per day as established in the original assessment also pertains to pregnant and breastfeeding women as well as to young children (i.e. toddlers) and infants. The corresponding margins of exposure (i.e. the ratio between the NOAEL and the maximum anticipated daily intakes) are 284 for infants, 236 for young children and 610 for pregnant and breastfeeding women. These margins of exposure are considered sufficient. The Panel concludes that the novel food, synthetic L-ergothioneine, is safe under the proposed uses and use levels for infants, young children (i.e. toddlers) and pregnant and breastfeeding women.

Keywords: L-ergothioneine, novel foods, food supplements

Requestor: European Commission

Question numbers: EFSA-Q-2017-00448

Correspondence: nda@efsa.europa.eu

Panel members: Jean-Louis Bresson, Barbara Burlingame, Tara Dean, Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Kristina Pentieva, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Daniel Tomé, Dominique Turck, Henk van Loveren, Marco Vinceti and Peter Willatts.

Acknowledgements: The Panel wishes to thank Davide Arcella for the support provided to this scientific opinion.

Suggested citation: EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), Turck D, Bresson J-L, BurlingameB, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, Mangelsdorf I, McArdle HJ, Naska A, Neuhäuser-BertholdM, Nowicka G, Pentieva K, Sanz Y, Siani A, Sjödin A, Stern M, TomédD, VincetiM, Willatts P, Engel K-H, Marchelli R, Pöting A, Poulsen M, Schlatter JR, Ackerl R and van Loveren H, 2017. Statement on the safety of synthetic L-ergothioneine as a novel food – supplementary dietary exposure and safety assessment for infants and young children, pregnant and breastfeeding women. EFSA Journal 2017;15(11):5060, 9 pp. https://doi.org/10.2903/j.efsa.2017.5060

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, an agency of the European Union.

Summary

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to provide a supplementary dietary exposure and safety assessment for synthetic L-ergothioneine for infants and young children, pregnant and breastfeeding women.

In 2016, the EFSA NDA Panel assessed the safety of synthetic L-ergothioneine as a novel food (NF) pursuant to Regulation (EC) No 258/97, and a Scientific Opinion was adopted on 26 October 2016. In performing the safety assessment of the NF, the NDA Panel considered the proposed uses (as a food ingredient added to alcohol-free beverages, milk, 'fresh' dairy products, cereal bars and chocolate; and as a food supplement) and the proposed target population, i.e. children above 3 years of age and the general adult population, with the exception of pregnant and breastfeeding women. Taking into account a no-observed-adverse-effect level (NOAEL) of 800 mg/kg body weight (bw) per day and the maximum estimated intake levels for L-ergothioneine from all sources (i.e. fortified foods, food supplements and background diet), in 2016, the Panel concluded that the margins of safety of 470 for adults (excluding pregnant and breastfeeding women) and of 216 for children above 3 years of age are sufficient.

In 2017, some Member States raised concerns about the potential for exposure of the excluded population subgroups to the NF from the consumption of products containing the NF, since in real life situations it would be difficult to ensure that those products (e.g. chocolate, dairy products) will not be consumed by the excluded subgroups.

In consequence, the European Food Safety Authority (EFSA) was asked to carry out a supplementary dietary exposure and safety assessment for L-ergothioneine for those groups of the population, i.e. infants and young children, pregnant and breastfeeding women, not considered in the previous assessment.

In order to derive intake estimates for these population groups, a refined intake assessment was performed by EFSA using the EFSA Comprehensive European Food Consumption Database, which is based on data from EU dietary surveys.

Food supplements as a source of the NF are not considered for the combined intake for these population groups, since for food supplements labelling is considered an effective means to restrict consumption by the target population (i.e. children above 3 years of age and adults excluding pregnant and breastfeeding women) of the NF. Moreover, no separate intake assessment was performed for pregnant and breastfeeding women, as consumption data for this population group are not available. However, it is considered that the expected intake of pregnant and breastfeeding women falls within the intake estimates calculated for the general adult population.

Combined intake estimates were calculated for L-ergothioneine from foods fortified with the NF and for naturally occurring L-ergothioneine from the background diet and maximum anticipated daily intakes were calculated as 2.82 mg/kg bw per day for infants, 3.39 mg/kg bw per day for toddlers and 1.31 mg/kg bw per day for adults including pregnant and breastfeeding women.

The Panel considers that based on the overall toxicological data the NOAEL of 800 mg/kg bw per day as established in the original assessment also pertains to pregnant and breastfeeding women as well as to young children (i.e. toddlers) and infants.

The corresponding margins of exposure (i.e. the ratio between the NOAEL and the maximum anticipated daily intakes) are 284 for infants, 236 for young children and 610 for pregnant and breastfeeding women. These margins of exposure are considered sufficient.

The Panel concludes that the NF, synthetic L-ergothioneine, is safe under the proposed uses and use levels for infants, young children (i.e. toddlers) and pregnant and breastfeeding women.

Table of contents

1. Introduction

1.1. Background

On 26 October 2016, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) adopted the Scientific Opinion on the safety of synthetic L-ergothioneine as a novel food (NF) pursuant to Regulation (EC) No 258/97[1] (EFSA NDA Panel, 2016).

In its opinion, the NDA Panel concluded that the NF, synthetic L-ergothioneine, is safe under the intended conditions of use as specified by the applicant, i.e. the NF to be added to various food groups (i.e. alcohol-free beverages, milk, 'fresh' dairy products, cereal bars and chocolate) and to be used as a food supplement. The target population was children above 3 years of age and the general adult population, with the exception of pregnant and breastfeeding women.

At the Standing Committee meeting held in March 2017, some Member States raised concerns about the potential for exposure of the excluded population subgroups to L-ergothioneine from the consumption of products containing L-ergothioneine. These Member States argued that although the use of L-ergothioneine has been assessed by EFSA to be safe for the intended uses as set out in the application, in real life situations it would be difficult to ensure that those products (e.g. chocolate, dairy products) will not be consumed by the excluded subgroups.

In consequence, it was decided that an exposure and safety assessment was needed for these excluded subgroups for additional reassurance.

1.2. Terms of Reference as provided by the requestor

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002, the European Commission asked the European Food Safety Authority to carry out a supplementary dietary exposure and safety assessment for L-ergothioneine for those groups of the population (infants and young children, pregnant and breastfeeding women) excluded by the applicant, as a novel food ingredient in the context of Regulation (EC) No 258/97.

2. Data and methodologies

2.1. Data

The supplementary dietary exposure and safety assessment of synthetic L-ergothioneine for infants and young children, pregnant and breastfeeding women is based on the data provided in the original NF application (i.e. Dossier 'Tetrahedron Ergoneine Documentation February confidential'), additional information submitted by the applicant in the context of the original application, and on the published Scientific Opinion on the safety of synthetic L-ergothioneine as a novel food (EFSA NDA Panel, 2016).

For the supplementary intake assessment, the EFSA Comprehensive European Food Consumption Database was used (EFSA, 2011).

2.2. Methodologies

The assessment follows the methodology set out in Commission Recommendation 97/618/EC of 29 July 1997 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.

3. Assessment

On 26 October 2016, the EFSA NDA Panel adopted the Scientific Opinion on the safety of synthetic L-ergothioneine as a novel food (NF) pursuant to Regulation (EC) No 258/97 (EFSA NDA Panel, 2016).

In performing the safety assessment of the NF, the NDA Panel considered the proposed uses (i.e. food ingredient added to alcohol-free beverages, milk, 'fresh' dairy products, cereal bars and chocolate; food supplements) and the proposed target population (i.e. children above 3 years of age and the general adult population, with the exception of pregnant and breastfeeding women).

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

Detailed information on the safety assessment of synthetic L-ergothioneine is provided in the published opinion (EFSA NDA Panel, 2016), which informs on the specifications of the NF, its stability, the production process, the anticipated intake/extent of use in the proposed target population, nutritional information of the NF, microbiological information, toxicological information (including absorption, distribution, metabolism and excretion), human studies and potential allergenicity of the NF.

In 2016, the NDA Panel considered a no-observed-adverse-effect level (NOAEL) of 800 mg/kg body weight (bw) per day of the NF. Taking into account this NOAEL and the maximum estimated intake levels for L-ergothioneine from all sources (i.e. fortified foods, food supplements and background diet) of 1.7 mg/kg bw per day for adults and of 3.7 mg/kg bw per day for children, the Panel concluded that the margins of safety of 470 for adults (excluding pregnant and breastfeeding women) and of 216 for children above 3 years of age are sufficient.

The scope of this scientific statement is to provide a supplementary dietary exposure and safety assessment of the NF for those groups of the population which had not been considered in the original safety assessment, i.e. infants and young children, pregnant and breastfeeding women.

3.1. Anticipated intake/extent of use

It is noted that the intended uses and use levels for the NF remain the same as in the original application, i.e. the applicant intends to use the NF in alcohol-free beverages, milk, 'fresh' dairy products (e.g. cream, cream cheese and yoghurts), cereal bars and chocolate (Table 1).

A quantity of up to 5 mg NF per serving of these foods was proposed. In order to achieve this quantity, the different food categories are proposed to be fortified with the NF at various use levels as indicated in Table 1, taking into account the various portion sizes of the foods. The indicated use levels represent the maximum use levels in the specified food groups.

Table 1: Proposed uses and maximum use levels of the NF as a food ingredient

Food category	Maximum use level of the NF (mg/kg)	Mean portion size
Alcohol-free beverages	25	200 mL
Milk	25	200 mL
'Fresh' dairy products	40	125 g
Cereal bars	200	25 g
Chocolate	250	20 g

The applicant also proposes to market the NF as a food supplement, with a recommended daily dose of up to 30 mg/day for adults excluding pregnant and breastfeeding women and 20 mg/day for children from 3–17 years.

Food supplements as a source of the NF are not considered for the population groups under evaluation for this statement, since for food supplements labelling is considered an effective means to restrict consumption by the target population (i.e. children above three years of age and adults excluding pregnant and breastfeeding women).

3.1.1. Intake from fortified foods

In order to derive intake estimates for the population groups under evaluation a refined intake assessment was performed by EFSA using the EFSA Comprehensive European Food Consumption Database (EFSA, 2011), which is based on data from EU dietary surveys.

The food categories for the proposed use of the NF were allocated to corresponding food categories of the EFSA Comprehensive Food Consumption Database (EFSA, 2011) as indicated in Table 2.

Table 2: Proposed uses and maximum use levels of the NF as a food ingredient considering the food categories of the EFSA Comprehensive Food Consumption Database

Food category used for the EFSA Comprehensive Data Base	Use levels (mg/kg)
Flavoured drinks with sugar	25
Flavoured drinks with sweetener	25
Unflavoured pasteurised and sterilised (including UHT) milk	25
Cream and cream powder	40
Flavoured fermented milk products including heat-treated products	40
Unflavoured fermented milk products, including natural unflavoured buttermilk (excluding sterilised buttermilk) non heat-treated after fermentation	40
Cereal bars	200
Cocoa and chocolate products	250

Mean and high (i.e. 95th percentile) intake estimates were calculated for infants, young children (i.e. toddlers) and adults (including pregnant and breastfeeding women), assuming that the foods contain the NF at the maximum proposed use levels.

No separate intake assessment was performed for pregnant and breastfeeding women, as consumption data for this population group are not available. However, it is considered that the expected intake of pregnant and breastfeeding women falls within the intake estimates calculated for the general adult population.

The ranges of the estimated mean and high intakes (in mg/kg bw per day) among the individual EU dietary surveys for the various population groups are presented in Table 3.

Table 3: Intake estimates of the NF from foods fortified with the NF at the maximum proposed use levels

Population group	Range of means (mg/kg bw per day)	Range of high intakes (95%)[(a)] (mg/kg bw per day)
Infants (up to 1 year)	0.11–1.39	0.40–2.82
Toddlers (i.e. young children) (1–3 years)	0.74–1.14	1.73–2.28
Adults (18–64 years) including pregnant and breastfeeding women	0.07–0.25	0.19–0.61

bw: body weight.
(a): Based on surveys with >60 consumers

3.1.2. Intake from the background diet

As described in the published opinion (EFSA NDA Panel et al., 2016), the foods with the highest natural L-ergothioneine content are mushrooms, which account for about 95% of naturally occurring L-ergothioneine intake via the diet.

Based on the available data, highest chronic exposures to natural L-ergothioneine were found for Italy for both population groups, adults and children.

For Italian adults, a mean and high (95th percentile) consumption of 0.06 and 0.48 mg/kg bw per day, respectively, was derived for the total population. In the population of consumers, mean and high consumptions amount to 0.22 and 0.70 mg/kg bw per day, respectively.

For the population of Italian children, a mean and high consumption of 0.06 and 0.64 mg/kg bw per day, respectively, was calculated for the total population, with a mean and high consumption for consumers of 0.41 and 1.11 mg/kg bw per day, respectively.

3.1.3. Combined intake from fortified foods and the background diet

Combined intake estimates were calculated for L-ergothioneine (synthetic and natural) from foods fortified with the NF and from the background diet.

A conservative approach was taken, summing up the highest 95th percentile intakes from fortified foods for each population group with the highest 95th percentile of intake of naturally occurring L-ergothioneine from the background diet (Table 4).

Table 4: Combined intake estimates (in mg/kg bw per day) for L-ergothioneine

Population group	Fortified foods95th percentile	Background diet95th percentile	Combined intake
Infants (up to 1 year)	2.82	– [(a)]	**2.82**
Toddlers (1–3 years)	2.28	1.11	**3.39**
Adults including pregnant and breastfeeding women	0.61	0.70	**1.31**

(a): In infants, the intake of L-ergothioneine via the background diet is considered negligible, as infants are not expected to consume mushrooms to a significant extent.

4. Discussion

In the original dossier, a NOAEL of 800 mg/kg bw per day of the NF was identified based on a 90-day toxicity study (according to OECD Test Guideline (TG) 408). In addition, in a screening test for reproductive and developmental toxicity (according to OECD TG 422), no effects of the NF on any parameter of reproductive or developmental toxicity were noted.

The Panel considers that based on the overall toxicological data the NOAEL of 800 mg/kg bw per day as established in the original assessment also pertains to pregnant and breastfeeding women as well as to toddlers (i.e. young children) and infants.

The maximum anticipated daily intakes of L-ergothioneine from the NF, in addition to the background diet, for infants, toddlers and adults including pregnant and breastfeeding women are 2.82, 3.39 and 1.31 mg/kg bw per day, respectively.

The corresponding margins of exposure (i.e. the ratio between the NOAEL and the maximum anticipated daily intakes) for the different population groups are presented in Table 5.

Table 5: Margins of exposure between the NOAEL (i.e. 800 mg/kg bw per day) and the combined intake estimates

Population group	Maximum anticipated intake (mg/kg bw per day)	Margin of exposure
Infants (up to 1 year)[(a)]	2.82	**284**
Toddlers (1–3 years)	3.39	**236**
Pregnant and breastfeeding women	1.31	**610**

bw: body weight.
(a): The NF is not intended to be added to infant formula.

The Panel notes the margins of exposure of 284 for infants, 236 for toddlers and 610 for pregnant and breastfeeding women.

These population groups can reasonably be expected not to consume the NF as a food supplement owing to labelling provisions.

The intake estimates are based on the conservative assumption that all proposed food items consumed by an individual contain the NF at the maximum proposed use levels. These estimates also consider high chronic intake of naturally occurring L-ergothioneine via the background diet, with the exception of infants, who are not expected to consume mushrooms (i.e. the main source of naturally occurring L-ergothioneine) to a significant extent with their diet.

The Panel considers that the margins of exposure for the NF at the intended uses and use levels are sufficient for infants, young children (i.e. toddlers) and pregnant and breastfeeding women.

5. Conclusions

The Panel concludes that the novel food, synthetic L-ergothioneine, is safe under the proposed uses and use levels for infants, young children (i.e. toddlers) and pregnant and breastfeeding women.

Documentation provided to EFSA

1) Letter from the European Commission to the European Food Safety Authority with the request to carry out a supplementary dietary exposure and safety assessment to L-ergothioneine. Ref. Ares(2017)2555205, dated 19/5/2017.

References

EFSA (European Food Safety Authority), 2011. Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment. EFSA Journal 2011;9(3):2097, 34 pp. https://doi.org/10.2903/j.efsa.2011.2097

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), Turck D, Bresson J-L, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, Mangelsdorf I, McArdle HJ, Naska A, Neuhäuser-Berthold M, Nowicka G, Pentieva K, Sanz Y, Siani A, Sjödin A, Stern M, Tomé D, Vinceti M, Willatts P, Engel K-H, Marchelli R, Pöting A, Poulsen M, Schlatter J, Ackerl R and Van Loveren H, 2016. Scientific opinion on the safety of synthetic L-ergothioneine (Ergoneine®) as a novel food pursuant to Regulation (EC) No 258/97. EFSA Journal 2016;14(11):4629, 27 pp. https://doi.org/10.2903/j.efsa.2016.4629

Abbreviations

bw	body weight
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NF	novel food
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
TG	Test Guideline