SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 4 April 2017

doi: 10.2903/j.efsa.2017.4778

Statement on the safety of EstroG-100™ as a novel food pursuant to Regulation (EC) No 258/97

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Abstract

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to update its scientific opinion on the safety of EstroG-100™ as a novel food (NF) in the light of additional information submitted by the applicant. In its previous scientific opinion of 2016, the Panel concluded that EstroG-100™, which is a hot-water extract of a mixture of three herbal roots, is safe for the use in food supplements at the maximum intake level of 175 mg/day in post-menopausal women, which is lower than the maximum intake level proposed by the applicant (514 mg/day). The Panel reached its conclusions based on the effects of EstroG-100™ on liver and haematology as observed in several oral toxicity studies, the lack of information on liver and haematological parameters in human studies and the absence of chronic toxicity data. In view of the Panel's conclusion on the safety of EstroG-100™, the applicant has now provided additional information on haematological and liver parameters for the human intervention study with EstroG-100™ and historical control data related to the subchronic 90-day oral toxicity study with EstroG-100™. After assessing the additional information provided by the applicant, the Panel considers that the conclusion of the scientific opinion on the safety of EstroG-100™ does not need to be revised, and thus, the Panel reconfirms that the NF is safe for the use in food supplements at the maximum intake level of 175 mg/day in post-menopausal women.

Keywords: EstroG-100™, *Cynanchum wilfordii*, *Phlomis umbrosa*, *Angelica gigas*, novel food, safety

Requestor: European Commission following the provision of additional information by Naturalendo Tech Co., Ltd

Question number: EFSA-Q-2017-00040

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Suggested citation: 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 JR, Turla E and van Loveren H, 2017. Statement on the safety of EstroG-100™ as a novel food pursuant to Regulation (EC) No 258/97. EFSA Journal 2017;15(5):4778, 8 pp. https://doi.org/10.2903/j.efsa.2017.4778

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 update its scientific opinion on the safety of EstroG-100™ as a novel food (NF) in the light of additional information submitted by the applicant.

EstroG-100™ is a hot-water extract of a mixture of three herbal roots (*Cynanchum wilfordii* Hemsley, *Phlomis umbrosa* Turcz. and *Angelica gigas* Nakai), which is concentrated and spray-dried. In its previous scientific opinion of 2016, the Panel concluded that EstroG-100™ is safe for the use in food supplements at the maximum intake level of 175 mg/day in post-menopausal women, which is lower than the maximum intake level proposed by the applicant (514 mg/day). The Panel reached its conclusions based on the effects of EstroG-100™ on liver and haematology (liver weight, reticulocytes, erythrocytes, albumin and total protein levels) as observed in several oral toxicity studies, the lack of information on liver and haematological parameters in human studies and the absence of chronic toxicity data. In particular, the effects of EstroG-100™ on liver were observed in a 28-day and 90-day oral toxicity study with EstroG-100™, and in 90-day oral toxicity studies with two of the three single constituents of EstroG-100™.

In view of the Panel's conclusion on the safety of EstroG-100™, the applicant has now provided additional information on haematological and liver parameters for the human intervention study with EstroG-100™ and historical control data related to the subchronic 90-day oral toxicity study with EstroG-100™.

The Panel considers that historical control data may be used to assess the validity of the concurrent control group but do not *per se* invalidate the findings in an animal experiment, in particular if these findings were supported by those in other relevant studies.

The data provided on the human intervention study with EstroG-100™, which lasted only 12 weeks, reported no changes in liver and haematological parameters. However, the Panel considers that the absence of changes in liver parameters in the short-period human intervention study is not enough to dismiss the concerns on the effects of EstroG-100™ on liver which were consistently observed in four repeated-dose oral toxicity studies (28-day and 90-day oral toxicity studies with EstroG-100™ and 90-day oral toxicity studies with two of the three single constituents of EstroG-100™). Likewise, the absence of changes in haematological parameters in the same human intervention study is not enough to dismiss the concerns from the Panel on the effects of EstroG-100™ on haematological parameters which were observed in the subchronic 90-day toxicity study with EstroG-100™.

Thus, the Panel reconfirms that the no-observed-adverse effect level (NOAEL) derived from the subchronic 90-day oral toxicity study with EstroG-100™, which was supported by observations in other studies, is 500 mg/kg body weight (bw) per day. By applying the uncertainty factor of 200 to the NOAEL, the Panel has derived the maximum intake level of 2.5 mg/kg bw per day for the NF, which corresponds to 175 mg/day for an adult of 70 kg bw.

After assessing the additional information provided, the Panel considers that the conclusion of the scientific opinion on the safety of EstroG-100™ does not need to be revised and thus the Panel reconfirms that the NF is safe for the use in food supplements at the maximum intake level of 175 mg/day in post-menopausal women.

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1. Introduction

1.1. Background

On 21 September 2016, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) adopted the Scientific Opinion on the safety of an extract of three herbal roots (EstroG-100™) as a novel food ingredient in food supplements pursuant to Regulation (EC) No 258/97[1] (EFSA NDA Panel, 2016).

In that scientific opinion, the Panel concluded that, based on the existing data, the margin of safety is not sufficient at the maximum intake level proposed by the applicant.

The applicant has now provided additional information. In consequence, the applicant is asking to review the additional information provided and, if necessary, to update the Scientific Opinion on the safety of EstroG-100™ as a novel food (NF) ingredient in food supplements.

1.2. Terms of Reference as provided by the European Commission

In view of the above, the European Commission requests the European Food Safety Authority (EFSA) to review the additional information provided by the applicant and, if necessary, to update the conclusions of the Scientific Opinion on EstroG-100™.

2. Data and methodologies

2.1. Data

The assessment of the safety of EstroG-100™ is based on the additional information provided by the applicant on EstroG-100™ as annexed to this Mandate.

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 21 September 2016, the NDA Panel adopted a Scientific Opinion on the safety of an extract of three herbal roots (EstroG-100™) as a NF in food supplements pursuant to Regulation (EC) No 258/97 (EFSA NDA Panel, 2016).

In that scientific opinion, the Panel concluded that EstroG-100™ is safe for the use in food supplements at the maximum intake level of 175 mg/day in post-menopausal women, which is lower than the maximum intake level proposed by the applicant (514 mg/day). The Panel reached its conclusions based on the effects of EstroG-100™ on liver and haematology as observed in several oral toxicity studies, the lack of information on liver and haematological parameters in human studies and the absence of chronic toxicity data.

In view of the conclusion on the safety of EstroG-100™, the applicant has now provided additional information on haematological and liver parameters for the human intervention study by Chang et al. (2012) and historical control data related to the subchronic 90-day oral toxicity study with EstroG-100™ (Biotoxtech Co, 2015).

In the context of this new Mandate, the applicant has also provided an expert report on the safety assessment of EstroG-100™ based on the available repeated-dose toxicity studies, which were already assessed by the Panel in September 2016, and the registration status of EstroG-100™ since its submission as a NF. The Panel considers that the review of the already assessed data and information on the registration status of EstroG-100™ do not provide any additional information on the safety of EstroG-100™.

[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.

3.1. Haematological and liver parameters

As reported in the adopted scientific opinion on EstroG-100™, the Panel has assessed the double-blind, placebo-controlled study by Chang et al. (2012), in which 64 women with menopausal symptoms were randomised to receive either EstroG-100™ (n = 31; 514 mg/day) or placebo (n = 33) for 12 weeks (EFSA NDA Panel, 2016).

The applicant has now provided the results on haematological and liver parameters for this human intervention study. In this respect, the Panel highlights that it is the duty of applicants to provide all available scientific data that are pertinent to the safety of NF when submitting applications for NF.

Baseline and week-12 values of the following haematological and liver parameters have been presented for each study group (EstroG-100™ and placebo): white blood cells, neutrophils, red blood cells, haemoglobin, platelets, mean corpuscular volume (MCV), bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, total protein, albumin, alkaline phosphatase and blood urea nitrogen.

The applicant indicated that there was no 'clinically significant increase' in liver parameters and no 'clinically significant changes' in haematological parameters in the EstroG-100™ group.

3.2. Historical control data

As reported in the adopted scientific opinion on EstroG-100™, the Panel has assessed the subchronic 90-day oral toxicity with EstroG-100™ (doses of 0, 500, 1,000, or 2,000 mg/kg body weight (bw) per day) (Biotoxtech Co, 2015) in Crl:CD(SD) rats. In this study, statistically significant increases in absolute and relative liver weights, albumin and total protein levels were reported at doses of 1,000 and 2,000 mg/kg bw per day (EFSA NDA Panel, 2016). This study also reported dose-related increases in reticulocyte counts, which were statistically significant only at the dose of 1,000 mg/kg bw per day.

The applicant has now provided historical control data related to this subchronic 90-day oral toxicity study (Lee et al., 2012). The historical control data were collected from 11 toxicity studies in Crl:CD (SD) rats (n = 110 males; n = 110 females) over a period of 5 years at the Biotoxtech Co testing facility.

The applicant commented that albumin and total protein levels as well as reticulocyte counts reported in the subchronic 90-day toxicity study by Biotoxtech Co (2015) 'match with the historical control data', and thus, the applicant considered these findings as not adverse. Historical control data on absolute but not relative liver weights were provided.

4. Discussion

In the adopted scientific opinion on EstroG-100™, the Panel noted that the subchronic 90-day oral toxicity study by Biotoxtech Co (2015) reported statistically significant increases in absolute and relative liver weights, albumin and total protein levels in the EstroG-100™ high-dose and mid-dose groups (2,000 mg/kg bw and 1,000 mg/kg bw per day) as compared to the control group. A statistically significant increase in relative liver weight was also reported in a 28-day oral toxicity study in rats with EstroG-100™ at doses of 1,000 and 3,000 mg/kg bw per day as compared to the control group (TTC Inc., 2015). Other subchronic 90-day oral toxicity studies with the constituents of EstroG-100™ (*Angelica gigas* and *Cynanchum wilfordii* Hemsley) reported dose-related increases in absolute and relative liver weight, total protein and albumin levels (Yun et al., 2015; Biotoxtech Co, 2016). The subchronic 90-day oral toxicity study with EstroG-100™ also reported a dose-related increase in reticulocytes in females, statistically significant at the dose of 1,000 mg/kg bw per day as compared to control group, and a decrease in erythrocytes, accompanied by an increase in MCV and mean corpuscular haemoglobin in females at the dose of 2,000 mg/kg bw per day as compared to the control group.

The Panel reiterates that the effects of EstroG-100™ on liver (weight, albumin and total protein levels) were observed in the 28-day and 90-day oral toxicity studies with EstroG-100™, which showed a dose–response effect that increased with the duration of exposure as compared to the control group. Similar dose-related effects on liver were also observed in 90-day oral toxicity studies with two of the three single constituents of EstroG-100™.

Historical control data were recently provided by the applicant for the 90-day oral toxicity study with EstroG-100™ to show that albumin and total protein levels and reticulocyte counts in the test group match with the historical control data. However, the Panel considers that historical control data

may be used to assess the validity of the concurrent control group but do not *per se* invalidate the findings in an animal experiment, in particular if these findings were supported by those in other relevant studies.

The data recently provided by the applicant on the human intervention study by Chang et al. (2012), which lasted only 12 weeks, reported no changes in liver and haematological parameters. However, the Panel considers that the absence of changes in liver parameters in the short-period human intervention study is not enough to dismiss the concerns on the effects of EstroG-100™ on liver which were consistently observed in the above-mentioned four repeated-dose oral toxicity studies (i.e. statistically significant increases in liver weight, albumin and total protein levels in the EstroG-100™ groups as compared to the control group). Likewise, the absence of changes in haematological parameters in the same human intervention study is not enough to dismiss the concerns from the Panel on the effects of EstroG-100™ on haematological parameters which were observed in the subchronic 90-day toxicity study with EstroG-100™.

Thus, the Panel reconfirms that the NOAEL derived from the subchronic 90-day oral toxicity study with EstroG-100™ (Biotoxtech Co, 2015), which was supported by observations in other studies, is 500 mg/kg bw per day. By applying the uncertainty factor of 200 to the NOAEL, the Panel has derived the maximum intake level of 2.5 mg/kg bw per day for the NF, which corresponds to 175 mg/day for an adult of 70 kg bw.

5. Conclusions

After assessing the additional information provided, the Panel considers that the conclusion of the scientific opinion on the safety of EstroG-100™ does not need to be revised and thus the Panel reconfirms that the NF is safe for the use in food supplements at the maximum intake level of 175 mg/day in post-menopausal women.

Steps taken by EFSA

1) On 11 January 2017, EFSA received the letter from the European Commission with the request to review additional information in relation to the scientific opinion on the safety of an extract of three herbal roots (EstroG-100™) as a novel food ingredient. Ref. Ares(2017) 140603-11/1/2017.
2) On 19 January 2017, EFSA received from the European Commission the additional information concerning the request above.
3) During its meeting on 4 April 2017, the NDA Panel, having evaluated the additional data, adopted a statement on the safety of EstroG-100™ as a novel food pursuant to Regulation (EC) No 258/97.

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Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
bw	body weight
MCV	mean corpuscular volume
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NF	novel food
NOAEL	no-observed-adverse effect level