

Safety Assessment of an extract of herbal roots (EstroG-100)

Name of Applicant: Naturalendo Tech Co. Ltd

Contact person(s): Cedric Bourges, Nutraveris

Introduction

An application for the authorisation of a mixture of herbal extracts (EstroG-100) was submitted to the Food Safety Authority of Ireland (FSAI) by Naturalendo Tech Co. Ltd of South Korea in accordance with *Article 4* of the novel food Regulation (EC) No. 258/97. The application was accepted by the FSAI on March 13th, 2014.

The novel ingredient is an aqueous extract of the roots of a mixture of three plants, *Cynanchum wilfordii* Hemsley, *Phlomis umbrosa* Turcz and *Angelica gigas* Nakai. None of these plants are known to have a history of consumption within the EU and are thus considered novel under EU legislation. The extraction is achieved using hot water followed by concentration and finally spray- or freeze-drying.

The applicant intends to market the novel ingredient in food supplements targeting post-menopausal females at a recommended intake of 514 mg/day. The application dossier includes some information on potential health benefits that are not considered in this report but may be assessed under relevant EU legislation separately. The ingredient has not been used in food production previously in the EU and is classed by the applicant as novel in accordance with *Article 1.2(e)* of the novel food Regulation (EC) No 259/97: “foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating and breeding practices and which have a history of safe food use”.

The application dossier was prepared pursuant to Commission Recommendation 97/618/EC and Class 2 was considered most appropriate in order to assess the wholesomeness of EstroG-100; “Complex novel food from a non-GM source”, and sub-class (2) “the source of the novel food has no history of food use in the Community”.

I. Specification of the novel food

EstroG-100 is characterised as a yellow to brown powder. The novel ingredient is cited as an aqueous extract of a mixture of three plants in similar proportions; *Cynanchum wilfordii* Hemsley (32.5%), *Phlomis umbrosa* Turcz (32.5%) and *Angelica gigas* Nakai (35%). Product specifications are provided which include specific chemical markers used to define the individual plant extracts. Heavy metal

and microbial levels are also provided and supported by batch analysis results as they are for dioxins, mycotoxins and certain pesticides.

Stability at room temperature has been established at three years. The applicant declares the novel ingredient to be “free of allergens” based on the fact that none of the three plants are known allergens and that no excipients are used. In addition, the applicant notes that two human studies did not reveal any adverse effects from the consumption of this novel ingredient while a long history of consumption in Asia has not identified any allergenic effect.

Effect of the production process applied to the novel food

The production of EstroG-100 is carried out by infusion (extraction) where the mixture of plant root material is allowed to steep in water heated to 95 °C for four hours. The aqueous solution is then filtered, concentrated and heat treated, after which it is spray/freeze dried to yield the final product.

II. History of the source organism

The individual herbal sources of EstroG-100 do not have a history of consumption within the EU but are common in traditional foods in Korea and China. The herbal root mixture that makes up EstroG-100 has been consumed in Korea for many years and is more recently on the market in Singapore, India and North America (USA & Canada).

IX. Anticipated intake/extent of use of the novel food

The original dossier stipulated that the applicant intended to market the novel ingredient in the EU in the form of food supplements to pre-, peri- and post-menopausal women with a recommended daily intake of 514 mg. However, the applicant subsequently clarified that the target population is post-menopausal women only and that the product label would carry the following advice: “This product is intended for post-menopausal women”. The dossier is not clear in the recommended duration of supplementation, though it is suggested that this will vary on a case by case basis.

X. Nutritional information on the novel food

The novel ingredient is not intended as a significant source of nutrients and from the information provided in the dossier its nutritional value is limited. Moderate amounts of macronutrients including carbohydrate, protein and fibre are present, while the levels of those micronutrients measured are unremarkable. The number of human studies is limited and most are short in duration with relatively small sample sizes. Nevertheless, these studies do not suggest that there is a nutritional impact from the consumption of the novel ingredient.

XI. Microbiological information on the novel food

The microbiological status of the novel ingredient is controlled by product specifications and supported by batch test results.

XII. Toxicological information on the novel food

Contaminants

Levels of lead, arsenic, cadmium and mercury were within regulatory limits and are controlled by specifications for the individual plant sources as well as the final EstroG-100, as confirmed by batch test results. Mycotoxin contamination was considered by the applicant and zearalenone, patulin, ochratoxin A, fumonisins, aflatoxin M1 and deoxynivalenol were not detected. Aflatoxin B1 was detected but was within EU regulatory limits. Pesticides were not detected in three lots of the novel ingredient sampled. As hot water is the only extraction medium used, organic solvent residues are not of concern. The applicant states that the novel ingredient complies with EU legislation governing contaminants such as dioxins and provided data confirming the absence of the radioactive markers iodine (I^{131}) and caesium ($Cs^{134} + Cs^{137}$).

Acute toxicity

The applicant provided results of a single oral dose toxicity study of EstroG-100 in Sprague-Dawley rats. The animals were administered EstroG-100 via oral gavage at doses up to a maximum of 4,000 mg/kg body weight, observed for 14 days and then sacrificed and necropsied. The only clinical sign of a treatment-related effect was compound-coloured stool in all animals and soft stool in 3 animals on the day after dosing. These findings were not recorded from day 2 onwards and were therefore considered not to have toxicological relevance. The lethal dose of EstroG-100 was reported at > 4,000 mg/kg body weight.

Sub-chronic toxicity

The results of a peer-reviewed 13-week oral gavage study on the effects of EstroG-100 in rats were provided. The animals were administered a product made up of 41% EstroG-100 along with seaweed calcium, L-arginine, L-lysine, soy extract powder and vitamins. The rats received varying doses of EstroG-100 (103, 206 and 412 mg/kg bw/day) daily for 13 weeks after which they were sacrificed and subjected to a full histopathological evaluation. No treatment-related mortalities or other adverse effects were recorded. No significant changes in a number of haematological parameters were recorded at any dose level. Where a dose-related trend was evident, such as the decrease in the differential eosinophil count in males, this was sex-specific and not corroborated by other findings. Statistically significant changes in clinical chemistry were recorded in males (creatinine kinase at 250 mg/kg bw/day and calcium at 1,000 mg/kg bw/day) and females (calcium at 250 mg/kg bw/day). However, there was no dose-response evident, the changes were reported to be within normal physiological limits and they were not corroborated by histopathological findings and were

therefore not considered to be toxicologically significant. Histopathology was unremarkable and a significant decrease in brain weight in high-dose males was not corroborated by changes in relative brain weight and was not recorded in females. The NOAEL was considered to be greater than 1,000 mg/kg bw/day (412 mg/kg bw/day of EstroG-100) for both sexes.

Mutagenicity

The mutagenic potential of EstroG-100 was investigated in three studies conducted to GLP, with no particular concerns identified. The Ames test was conducted using one *E. coli* and four Salmonella strains that were exposed to various doses of EstroG-100 (maximum 5,000 µg/plate). Growth inhibition or test substance precipitation was not observed in the presence or absence of metabolic activation and the numbers of revertants in the test plates were less than the negative controls.

The mutagenic potential of EstroG-100 (maximum 5,000 µg/ml) was also studied in Chinese hamster lung cells using an *in vitro* chromosome aberration assay. The frequency of chromosomal aberrations in the test groups was less than 5% and no statistically significant increase compared to the negative control was recorded.

An *in vivo* micronucleus test in young male mice that were gavage fed with the novel ingredient (maximum 2,000 mg/kg) did not identify a genotoxic potential.

Human studies

The adsorption, distribution, metabolism and excretion of the novel ingredient has not been established or addressed in the dossier. The purported mitigation by EstroG-100 of menopausal symptoms in women is not a matter for this safety assessment. However, certain studies carried out to demonstrate efficacy of the novel ingredient can provide valuable safety information. Results of a study submitted by the applicant demonstrated that the novel ingredient does not exhibit any binding affinity with the alpha (α) and beta (β) oestrogen receptors, though the precise mode of purported action has not been elucidated. A 2005 Korean study did not identify negative effects in menopausal women consuming Estromon, a product made up of 40.81% EstroG-100 along with seaweed calcium, L-arginine, L-lysine, soy extract powder, ferrous lactate and magnesium stearate, for 1 year. No adverse effects were recorded in the clinical study published in 2012 and conducted in the U.S. as a randomised, double blind placebo-controlled trial targeting non-Asian American women who were administered EstroG-100 for 12 weeks.

Allergenicity

The applicant declares that there is no history of allergenicity associated with any of the three plant species which are the sources of the novel ingredient. This, along with the lack of reports of allergic reactions in Asian countries where the product has a history of consumption provides some assurance that EstroG-100 is not a significant allergenic threat.

Conclusions

EstroG-100 is intended for use in the EU as a food supplement for post-menopausal women, with a daily recommended intake of 514 mg. EstroG-100 is not intended as a significant source of nutrients and the main reason for the application to market this product is related to the purported health benefits in relieving menopausal symptoms, even though the actual mechanism of action remains unknown at this time. The toxicological data provided have not revealed any significant safety concerns linked to the consumption of this novel ingredient. This, along with the history of safe consumption in Asia and its authorised presence on the market in North America provides a certain level of reassurance about the safety of EstroG-100 at the proposed use levels.

Recommendation

On the basis of the information provided in the application dossier, along with subsequent clarifications, the Food Safety Authority of Ireland has not identified any safety concerns with the consumption of food supplements containing EstroG-100 at the proposed use levels. Therefore, the FSAI considers that this novel ingredient, produced by Naturalendo Tech Co. Ltd., meets the criteria for novel food set out in *Article 3.1.* of the novel food Regulation (EC) No 258/97. Any products containing EstroG-100 should carry advice on the label that the product is only for consumption by post-menopausal women and further advice that it should not be consumed by pregnant or breast feeding women or children should be considered as a risk management measure.