Safety Assessment of Dried Aerial Parts of *Hoodia parviflora* (DHP)

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Novel food category: 1.2(e)

Introduction

An application for the authorisation of dried aerial parts of *Hoodia parviflora* (hereafter referred to as DHP) as a novel food ingredient was submitted to the Food Safety Authority of Ireland (FSAI) by Desert Labs, Ltd of Israel in accordance with *Article 4* of the novel food Regulation (EC) No. 258/97. The application was accepted by the FSAI on February 13th, 2015.

Hoodia parviflora is a succulent cactus-like milkweed plant of the *Apocynacea* family native to southern Africa. The stems of various *Hoodia* species have been consumed as a traditional food for many years by people indigenous to southern Africa with select species being consumed in the belief that they helped to control hunger. Though the plant grows naturally in the wild, as a conservation measure and for consistency, the *H. parviflora* plants used by Desert Labs as raw material are specially cultivated all year round in a particular region in Israel. The production process is carried out according to good manufacturing process standards and begins with the selection and cleaning of suitable aerial plant parts which are then dried or freeze-dried and powdered prior to packaging.

The applicant intends to market the novel ingredient in conventional foods targeting the adult population at a recommended intake of 120-245 mg/day. It is also intended for use in food supplements, providing a maximum of 245 mg/day (3.5 mg DHP/kg body weight per day).

The ingredient does not have a significant history of consumption in the EU before 1997 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(2) was considered most appropriate in order to assess the wholesomeness of DHP; "Complex novel food from a non-GM source"; "the source of the novel food has no history of food use in the Community".

I. Specification of the novel food

DHP is characterised as a bitter tasting light green to tan fine powder with less than 5% moisture content. Up to 80% of DHP is made up of carbohydrate, with dietary fibre constituting a significant proportion of that. Product specifications are provided which include physical and chemical parameters as well as specifications for contaminants such as heavy metals and select microorganisms. Routine analysis is also carried out on contaminants such as aflatoxins and pesticide residues. The applicant provides structural and quantitative data on the major steroid glycosides present in *H. parviflora*.

The applicant states that ELISA screening tests indicate that the proteins in DHP are not cross-reactive with some of the major food allergens and thus not likely to pose a significant allergenic risk. Furthermore, the applicant states that DHP has been marketed in the United States as an ingredient in dietary supplements since 2011 without concern, and that allergic reactions to any *Hoodia* species have not been reported to date.

The applicant has established that DHP remains within specification under normal storage conditions for 1 year while a five year stability study is ongoing.

II. Effect of the production process applied to the novel food

The production of DHP powder is carried out to GMP standards with HACCP controls in place. The process begins by excising the aerial parts of *H. parviflora* plants that are at least three years old and grown in Israel. The plant parts are sanitised in peroxyacetic acid or sodium dichloroisocyanurate and rinsed in tap water before being cut into pieces of 10-20cm in size, dried or freeze-dried and then ground into a powder. The powder is passed through a metal detector, packaged in double-sealed food grade bags and heat treated at 80°C for 6 hours to ensure it meets microbiological specifications.

III. History of the source organism

The applicant states that there are 13 species of plants within the *Hoodia* genus, though other sources put that number as high as 25 species. Many Hoodia plants have been used as a traditional food source by indigenous tribes in Southern Africa, with some consumed in the belief that they suppressed appetite. Research on the purported appetite-suppressing qualities of *Hoodia* species, particularly *H. gordonii* has been ongoing for some years resulting in a tentative linkage with certain steroid glycosides present in some *Hoodia* species. Though dietary supplements containing certain *Hoodia* species are on the US market since 2011, a significant history of consumption within the EU of any of the *Hoodia* species has not been demonstrated in food or supplements and so authorisation under the novel food Regulation is required.

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

DHP in foods and food supplements is intended as an aid for adults to suppress appetite and therefore is not intended for long term consumption. DHP will be marketed as an ingredient in foods including beverages, biscuits, confectionary, savoury snacks, soups and broths, tea, coffee and water at levels of 120-245 mg/serving. DHP is also intended for use in food supplements at levels up to 245 mg/day (3.5 mg/kg body weight). The applicant assumes that DHP supplements would be consumed as an alternative rather than in addition to DHP containing foods by people wishing to reduce their appetites and proposes a labelling strategy to avoid over-consumption. Although adults are the intended consumers of foods fortified with DHP, the applicant includes teenagers (12 years and older) in the exposure assessment using data from the UK National Diet and Nutrition Survey (NDNS) based on the upper maximum proposed intake levels across all the foods proposed for use. "All-person" (i.e. all individuals surveyed in the NDNS regardless of whether they would consume products that contain DHP or not) and "all-user" (i.e. those who consumed one or more foods proposed that contain DHP) intakes were considered.

The proposed intake levels vary across the different population groups and the higher intakes among male teenagers and female adults are to be anticipated given the range of foods to which DHP is to be added. The applicant does not refer to safe or unsafe dietary levels for DHP consumption, or even whether such information has been established. Therefore it is not clear whether the deduced intake levels are of more relevance to the safety of the product or to its efficacy in the purported suppression of appetite.

Notwithstanding this, a NOAEL has been established in experimental rats at 350 mg/kg bw/day, the highest dose tested and which is 100-fold above the level intended for human consumption. Extrapolating this NOAEL figure to humans, and taking the standard "10-fold safety factor" into account[i], it is reasonable to assume that even the highest 95th percentile intake (12.3 mg/kg bw/day) among "all-user" adult females falls within the margins of safety.

XI. Nutritional information on the novel food

The novel ingredient is not intended to replace any foods currently on the EU market. Though it is a source of nutrition, primarily carbohydrate (including fibre), the main target for this novel food is people wishing to suppress their appetite, a characteristic which is tentatively linked with the presence of steroid glycosides (hoodigosides) in some *Hoodia* species.

XII. Microbiological information on the novel food

The microbiological status of the novel ingredient is controlled by product specifications and supported by batch test results on microorganisms including *E. coli*, *Staphylococci*, *Salmonella*, *Listeria* yeasts and moulds.

XIII. Toxicological information on the novel food

(a) Adsorption, Distribution, Metabolism and Excretion (ADME)

DHP is a dried crude biomass of *H. parviflora* made up primarily of carbohydrate (70-80%), ash (14-19%) protein (2.5-4.5%) and steroid glycosides (approximately 1%) as well as micronutrients including vitamin and minerals. The fate of these constituents in the body is well established, except perhaps for the steroid glycosides which only make up approximately 1% of the novel food.

(b) Acute Toxicity

The applicant emphasised that acute studies are not specified in the SCF novel food guidance. Repeated dose rat studies for 14 days and 90 days did not indicate any acute negative effects and so they decided that acute dose preclinical studies would not provide any additional useful information. In support of this, the applicant cites the history of consumption of *Hoodia* plants by indigenous people in South Africa and their uneventful consumption as dietary supplements in the USA since 2011.

(c) Repeated dose toxicity studies

Sprague Dawley rats were fed DHP at up to 350 mg/kg bw/day in a 90-day feeding study. Reductions in body weight, body weight gain, and food consumption were observed in females receiving 250 and 350 mg/kg body weight and food consumption was reduced in males receiving 350 mg/kg bw/day. The changes in body weight parameters at doses of $\geq$ 250 mg/kg bw/day were not associated with adverse effects on tissues or on organ function. There were no adverse effects on haematological, clinical chemistry, coagulation or urinalysis parameters or on the results of the functional observational battery and histopathological examinations. The NOAEL for DHP was determined to be 350 mg/kg bw/day, the highest dose that could be tested.

(d) Reproductive Toxicity

Sprague-Dawley rats were administered DHP up to 350 mg/kg bw/day from 11 weeks prior to mating, through mating and gestation, and up to postnatal day 4. Significant decreases in body weight were noted in females receiving 250 or 350 mg/kg bw/day over gestational day (GD) 0 to 20, which did not negatively impact on pregnancy outcomes. Significant decreases in food consumption also were observed in females receiving 250 or 350 mg/kg bw/day during GD 0 to 7, which was accompanied by decreases in food efficiency.

Relative to controls, there were no apparent changes in oestrous cycle duration; evidence and time to mating; fecundity; gestation length; number of implantation sites; number of corpora lutea; pre- and post-implantation loss; litter weight; neonatal viability and sex ratio. There was no evidence of effects on spermatogenesis in treated rats compared to controls and all reproductive parameters recorded for treated dams were consistent with historical control ranges for Sprague-Dawley rats. There were no

clinical or congenital findings in the F1 generation that could be ascribed to treatment or dosing with DHP.

In conclusion, there is no evidence of any adverse effects on reproductive and developmental endpoints in rats treated with DHP up to a concentration of 350 mg/kg bw/day.

(e) Mutagenicity and Genotoxicity

An Ames study of the mutagenic potential of DHP at concentrations up to 5,000 µg/plate did not reveal any biologically relevant increases in revertants in any of the microbial strains either with or without metabolic activation. The genotoxicity of DHP was also assessed in an *in-vitro* micronucleus assay with no biologically relevant increase of micronuclei found at either the 4hr or 44hr time points. No statistically significant change in the number of cells with micronuclei was noted in the DHP-dosed groups. DHP was not found to induce structural or numerical chromosomal damage in human lymphocytes. Overall, the data indicates that DHP lacks *in-vitro* genotoxic potential at the concentrations tested, with no *in-vitro* evidence of gene mutations or structural and numerical chromosome aberrations. Based on a lack of adverse effects on reproductive and developmental endpoints, a NOAEL for DHP was determined to be 350 mg/kg bw/day, the highest dose tested.

Carcinogenicity

Carcinogenicity or long term studies on DHP were not provided by the applicant on the basis that there was no indication of mutagenic or genotoxic potential or of any adverse effects in a 90-day *in-utero* exposure study. In addition, the applicant contends that consumption of products containing *H. parviflora* is intended as a short term intervention rather than a long term weight maintenance strategy.

(f) Clinical trials

Two human intervention studies of DHP at levels of up to 284 mg/day did not identify any safety concerns. One study involved the administration of 34.4 mg DHP/kg bw/day for 30 days to subjects with insulin resistance and non-alcoholic fatty liver disease in which DHP was found to be well-tolerated, with no test article-related adverse effects recorded.

A second trial was conducted to evaluate the tolerance and safety of the fresh ground *H. parviflora* aerial parts in healthy normal weight, overweight, and obese adult subjects. The incidence of reported adverse events was slightly raised in the *Hoodia* treatment groups relative to the placebo controls. The adverse events were categorised as mild and transient including headaches, stomach cramps, indigestion/heartburn, nausea and changes in bowel function. Body weight loss, BMI reduction and changes in waist circumference were minor but statistically significant in normal weight, overweight and obese subjects receiving the *H. parviflora* frozen product compared to placebo controls.

(g) Allergenicity

The protein content of DHP can be up to 4.5% and enzyme-linked immunosorbent assay (ELISA) screening did not reveal cross-reactivity with some of the major food allergens including peanut, milk, egg, crustacean, gluten and soyabean. In addition, the applicant emphasises that since being marketed in the USA in 2011, there have been no reports of allergic reactions to DHP, nor have there been any reports in the literature to date of allergic reactions to any *Hoodia* species.

Conclusions

DHP is intended for use in the EU as a food ingredient at 120 to 245 mg/serving and in food supplements at a maximum of 245 mg/day (3.5 mg/kg body weight). The novel food is not intended to be a significant source of long term nutrition, but instead will be targeted at adults who wish to reduce their appetite, probably as part of a weight loss strategy. Some of the food categories to which DHP is to be added (confectionary and savoury snacks) have a minimal role in a healthy diet and it is challenging to see the merit in increasing the appeal of normally high-calorie foods for people trying to reduce their appetite and lose weight.

Anecdotal evidence and a number of peer-reviewed publications form the basis for claims about the ability of some *Hoodia* plants to suppress appetite. These claims are not addressed in this assessment as nutrition and health claims are governed by separate EU legislation.

The unmonitored consumption of *Hoodia* species by indigenous tribes in Southern Africa is of limited value in assessing the plant's safety. However, of greater value is the pharmacovigilence adverse effect reporting program which has been implemented since the introduction to the US marketplace of *H. parviflora*, where no adverse effects have been reported to date. A small number of published studies on animals and humans suggest possible adverse effects associated with the consumption of *Hoodia gordonii* extracts which contain high levels of steroid glycosides. However, those studies are of little relevance to the safety of DHP as they relate to the consumption of concentrated extracts of a different *Hoodia* species which has a relatively high content (>75%) of steroid glycosides compared to the dried whole plant material of *H. parviflora* with an average of 1% steroid glycoside content.

Some of the toxicological studies provided by the applicant indicate a distinct and significant effect (weight loss) associated with the consumption of *H. parviflora* at certain concentrations, and had appetite suppression not been an intended effect, such weight loss could be considered an adverse effect. However, appetite suppression is an intended effect of the consumption of foods and beverages containing DHP and the toxicological data does not identify any cause for concern arising out of the consumption as proposed. Human clinical trials using doses of up to approximately 3g/person/day were well tolerated and did not identify any significant test-article related adverse effects.

Though certain steroid glycosides present in *H. parviflora* are currently suggested to be a factor in appetite suppression, a possible mode of action or cause of the purported appetite suppression effect has yet to be elucidated. While such information may provide further reassurance on the safety of *Hoodia parviflora* consumption, it is likely to be more useful in demonstrating a cause and effect necessary for any potential health or nutrition claim approval in the EU.

Recommendation

On the basis of the information provided by the applicant, along with subsequent clarifications, the Food Safety Authority of Ireland has not identified any safety concerns with the consumption of foods or food supplements containing *Hoodia parviflora* at the levels proposed. However, consideration should be given to reducing the number of food categories to which DHP is to be added, for example confectionary and savoury snacks, unless such foods have a reduced calorie content by virtue of lower fat or sugar levels. This would have the dual effect of reducing the potential for over consumption of the novel ingredient and at the same time avoid adding appeal to high calorie foods. Adequate advice should be provided to indicate that the product is not suitable for children and only intended for consumption for a limited time period (6 months suggested by the applicant) by adults trying to lose weight.

Overall, the FSAI considers that this novel ingredient, produced by Desert Labs, Ltd of Israel meets the criteria for novel food set out in *Article 3.1.* of the novel food Regulation (EC) No 258/97.

[i] National Research Council (1994) Science & Judgement in Risk Assessment. Washington DC, National Academic Press