Summary of the application: CO2 extract from *Cannabis sativa* L.

Applicant: Charlotte's Web, Inc. Address: 1600 Pearl Street, Suite 300, CO 80302 Boulder, the United States of America.

Charlotte's Web (CW) hemp-derived CO_2 extract is the novel food under application which contains cannabidiol (CBD) at approximately 50%. The rest of the extract contains other cannabinoids, terpenes, non-cannabinoid lipids and carbohydrates. CW's hemp-derived CO2 extract is intended to be used diluted in oil (olive oil or medium chain triglycerides-MCT) as a food supplement and proposed for use by the general population above 3 years of age, excluding pregnant and lactating women. No literature was identified to raise concerns for the use of hemp extracts by pregnant and lactating women, nonetheless the restriction of use is taken by CW as a precautionary act.

CW´s hemp-derived extract is obtained by decarboxylation of hemp followed by CO_2 extraction of the hemp plant material. The manufacturing process of CW's hemp-derived CO_2 extract can be described as follows: 1. Hemp from fields located in the US are harvested, sampled and sent for extract processing. 2. In-house processes at the Charlotte's Web, Inc. LOFT produce Charlotte's Web hemp-derived CO_2 extract using ethanol as the solvent. 3. Raw hemp is delivered to the alcohol extraction process suites for extraction. Extract is produced by CO_2 extraction and is sampled, labelled, placed under the designation of Quality Control Hold, then transferred to a secure Work-In-Process (WIP) storage location until testing is returned and the extract can be released for use in finished products.

Charlotte's Web has performed genotoxicity testing and sub-chronic toxicity testing. The results were extrapolated from Charlotte's Web hemp-derived IPA extract to Charlotte's Web hemp-derived CO_2 extract. The genotoxicity of Charlotte's Web hemp-derived Isopropyl Alcohol (IPA) extract was assessed with a Good Laboratory Practices (GLP)-compliant bacterial reverse mutation test, conducted in accordance with Organisation for Economic Co-operation and Development (OECD) guideline 471 (1997). The results did not show evidence of bacterial mutagenicity, and the novel food is therefore considered to be non-mutagenic. The literature further supports that hemp-derived extracts obtained *via* supercritical CO_2 extraction are non-genotoxic and non-mutagenic (Marx et al. 2018).

A review of the literature showed that a standard battery of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use *(*ICH*)*/GLP-compliant genotoxicity tests have been conducted (Ames assay, *in vivo* micronucleus assay in rat and *in vivo* alkaline COMET assay) for the approval of CBD in the treatment of Dravet and Lennox-Gastaut syndrome in the US and the EU. Both the European Medicines Agency (EMA) and the United States Food & Drug Administration (US FDA) concluded that CBD was negative for mutagenicity and clastogenicity in adequately conducted assays (EMA 2019; (FDA 2018; GW-Pharma-Ltd 2019).

The subchronic toxicity of Charlotte's Web hemp-derived IPA extract was investigated in two GLP-compliant 14-day and 90-day toxicity studies. Studies were run following OECD Guideline No. 407 (2008) and OECD Guideline No. 408 (1997), respectively. In the 90-day oral toxicity study conducted by the applicant, the NOAEL for Charlotte's Web hemp-derived IPA extract (9%) in olive oil (91%) was 800 mg/kg bw/day for female and 400 mg/kg bw/day for male rats. By applying an uncertainty factor of 100, a safe dose (also known as ADI or acceptable daily intake) of 4 mg/kg bw/day of the diluted extract was calculated for Charlotte's Web hemp-derived IPA extract. This would equate to a safe

exposure of 0.46 mg of the CO2 hemp extract per kg bw/day (or 32.3 mg/day) and 0.23 mg CBD/ kg bw/day (16.2 mg per daily serving) per proposed daily serving for adults. In addition, an exhaustive subchronic ICH/GLP-compliant package was submitted for the approval of CBD – the main cannabinoid in CW's hemp-derived CO2 extract - for the treatment of Dravet and Lennox-Gastaut syndromes in the US and the EU. The NOAEL in the 26-week rat study was 150 mg CBD/kg bw/day. The corresponding safe dose applying a 100-times margin of safety is 1.5 mg CBD/kg bw/day.

Nevertheless, CBD, the main cannabinoid in Charlotte's Web hemp-derived extract, has been widely studied and shown to be administered up to single doses of 6,000 mg in healthy subjects in children and adults. Based on the studies with healthy subjects, a safe dose is considered between 400-700 mg CBD per day(EMA 2019; Jadoon et al. 2017; Ltd 2019; Manini et al. 2015; Martin-Santos et al. 2012; Schoedel et al. 2018; Taylor et al. 2018; Winton-Brown et al. 2011). Charlotte's Web hemp-derived CO2 extract will be marketed to the general population aged 3 years and older, excluding pregnant and lactating women as a precautionary measure. No literature was identified to raise concerns for the use of hemp extracts in these groups, nonetheless the restriction of use is wished to be taken by CW as a precautionary act.

CW's hemp-derived CO2 extract does not pose a safety risk to human health, on the basis of the safety tests performed. CW's hemp-derived CO2 extract has a maximum recommended dose of 0.46 mg/kg bw/day, which is x100 times less than the NOAEL established in the 90-day rat study conducted by the applicant. Overall, the information reviewed and provided in this application supports safety of Charlotte's Web hemp-derived CO2 extract as novel food under the proposed conditions of use and dose level.

References

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