

Summary of the application: Extract of *Cannabis sativa* L. extract with Tetrahydrocannabinol (THC) removed

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

Charlotte's Web (CW) THC removed hemp-derived extract is the novel food under application which contains cannabidiol (CBD) at approximately 93%. The rest of the extract contains other cannabinoids, terpenes, non-cannabinoid lipids and carbohydrates. CW's hemp-derived extract is intended to be used diluted in oil (olive oil or medium chain triglycerides-MCT) or as gummies or capsules 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 that would 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 CO₂ extraction of the hemp plant material followed by decarboxylation of the resulting hemp extract. The data presented in this dossier supports the safety of CW's hemp-derived extract under the proposed conditions of use.

The manufacturing process of CW's THC removed hemp-derived extract can be described as follows: 1. Hemp from fields located in the USA are harvested, sampled and sent for extract processing. 2. An external manufacturer produces Charlotte's Web hemp-derived CO₂ extract using ethanol as the solvent. 3. Raw hemp is delivered to the alcohol extraction process suites for extraction. Extract is produced by CO₂ extraction and is further winterised and decarboxylised. Finally, THC is remediated by distillation. The final extract is sampled, labelled, placed under the designation of Quality Control Hold, then transferred to a secure storage location until testing is returned and the extract can be released for use in finished products.

CW has performed genotoxicity testing and sub-chronic toxicity testing. The results were extrapolated from CW's hemp-derived Isopropyl Alcohol (IPA) extract to Charlotte's Web THC removed hemp-derived extract. The genotoxicity of CW's hemp-derived 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 CO₂ 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 CW's 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 CW's 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 CW's hemp-derived IPA extract. This would equate to a safe exposure of 0.26 mg of the THC removed hemp-derived extract per kg bw/day (or 18 mg/day) and 0.24 mg CBD/ kg bw/day (17 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 THC removed hemp-derived 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 CW's 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). CW's THC removed hemp-derived 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 extract used as an ingredient in food supplements will not mislead the consumers. The labelling will provide clear information on the recommended doses, amount of CBD per recommended dose, and a clear statement in regards to the target population to whom the food supplement will be marketed. The selling of CW's THC removed hemp-derived extract will comply with the EU laws on labelling and information to consumers as provided by Regulation 1169/2011 on the provision of food information to consumers and Directive 2002/46/EC on food supplements.

CW's THC removed hemp-derived extract does not pose a safety risk to human health, on the basis of the safety tests performed. CW's THC removed hemp-derived 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 CW's THC removed hemp-derived extract as novel food under the proposed conditions of use and dose level.

References

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