

Summary of application: Cannabidiol isolated from the Cannabis sativa L. plant

Applicant: Mile High Labs, 2555 W. Midway Boulevard, Broomfield, CO 80020, USA

This is an application for authorisation to place on the market, cannabidiol (CBD) isolated from the *Cannabis sativa* L. plant as a Novel Food in the European Union (EU). The application has been compiled in line with the administrative and scientific requirements of Regulation (EU) 2017/2469 for applications referred to in Article 10 of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. It is also in line with the European Food Safety Authority (EFSA) guidance on the preparation and presentation of an application for authorisation of a Novel Food in the Context of Regulation (EU) 2015/2283.

Mile High Labs has quality systems in place to ensure that the manufactured CBD isolate is consistent and safe for use as a novel food. The quality systems conform to ISO 9001:2015 and GMP standards. Each lot of CBD isolate is analysed to ensure that it meets the predetermined specification for CBD content as well as potential contaminants such as THC, residual solvents, pesticides, heavy metals and mycotoxins. The analytical methods employed are validated or, in the case of compendial methods, suitable for their intended use. The manufacturing and quality control systems, throughout the supply chain ensure that the CBD isolate meets a CBD purity of 98%.

The applicant followed EFSA's recommended tiered approach for the safety assessment using the applicant's CBD isolate as intended to be marketed. Bioavailability studies show that CBD appears rapidly in the plasma after oral intake. Similarly, literature studies report a time to maximum plasma concentration of 2.5-5 hours at steady state in humans with oral bioavailability enhanced in lipid-based vehicles. Literature studies also show that tissue distribution of CBD is extensive, presumably due to its high lipophilicity and that CBD is extensively metabolised in the liver via CYP450 and UDP-glucuronosyltransferase (UGT) enzymes. As such, CBD has the potential to alter liver enzymes involved in the metabolism of medicines.

The applicant's general toxicity studies revealed the liver as the target organ, as daily administration of CBD (98% pure) caused reversible dose-dependent liver changes. These findings were considered as non-adverse, as there was an absence of inflammation and necrosis. From the applicant's GLP 90-day oral study in the rat, the NOAEL is 150 mg/kg/day, after applying uncertainty factors (100-fold) this lowers to 1.5 mg/kg/day, equivalent to 105 mg/day in a 70 kg adult. Nevertheless, literature studies have shown that the NOAEL in a non-rodent species is 100 mg/kg/day, after applying uncertainty factors (100-fold) this lowers to 1 mg/kg/day. The latter, being the lower value, sets a recommended maximum daily dose of 1 mg/kg/day, equivalent to 70 mg/day in a 70 kg adult. The applicant's GLP tiered genotoxicity studies of CBD (98% pure) did not detect any mutagenic or clastogenic activity. From the literature, a carcinogenicity study in rats, over 104 weeks, showed that there was no evidence of CBD related increase in tumour incidences.

Literature data in humans, provide evidence that CBD is well tolerated with a good safety profile under the proposed conditions of use. No human data are available on the effect of CBD on fertility and there are limited data from the use of CBD in pregnant women. There are no clinical data on the presence of CBD or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. However, given that CBD is highly protein bound and lipophilic it will likely pass freely from plasma into milk.

In conclusion, based on the safety of the CBD isolate novel food under the proposed conditions of use, a recommended maximum daily dose of 1 mg/kg equivalent to 70 mg/day is proposed for healthy adults. As a precautionary measure, children, people on medication, pregnant and breast-feeding women should not consume CBD isolate.